

GARLIC

Allium sativum



Steven Foster

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Botanical Series - 311

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On the cover:

Garlic, *Allium sativum*. Photo ©1996 Steven Foster.

GARLIC

Allium sativum

by Steven Foster

It has been said that your food should be your medicine and your medicine should be your food. Garlic is perhaps the quintessential medicinal food. Known at least as long as humans have recorded historical events, perhaps no other plant has been used for so long, in as many cultures, and for as many medicinal and culinary purposes as garlic, Allium sativum.

Origins

Now known as a variable cultigen (found only in cultivation), garlic's wild progenitor is thought to have originated in the high plains of West-Central Asia (Kato, 1972). De Candolle places garlic's origin in the Kirgiz Desert of Western Russia. Garlic may have derived from the Central Asian species *A. longicupis* Regel (Mabberly, 1987). The plant spread east and west with nomadic tribes, and was known to be cultivated in the Middle East more than 5,000 years ago.

The word garlic originates from the Anglo-Saxon "gar-leac" or "spear-plant" (Pickering, 1879). "Allium," the ancient Latin name for garlic, is derived from the Celtic *all*, signifying hot or burning. The species name "sativum" means planted, cultivated or sown (not wild). The genus *Allium* of the lily family (Liliaceae) includes upwards of 700 species, including onions, chives, shallots, and leeks.

There are approximately 18,000 acres of garlic cultivated in the U.S. The 1989 garlic harvest in California, the major garlic-producing state, yielded about 250 million pounds. The vast bulk of the crop is used to produce dehydrated garlic products. About 50 million pounds of the California crop is sold as fresh garlic. Americans consume an estimated 80 million pounds of fresh garlic per year.

History

From the time of the Egyptian pharaohs and the earliest Chinese dynasties, garlic (*Allium sativum*) has been widely consumed as both food and medicine. Is garlic the secret key to the construction of the pyramids? Herodotus (484-425 B.C.), the Greek historian, known as the "Father of History," said that there is an inscription of Egyptian characters on a pyramid which records the quantities of radishes, onions, and garlic consumed by the laborers who constructed it (Manniche, 1989). Manniche notes the discovery of garlic cloves in the tomb of Tutankhamen, and the sacred animal temple precinct at Saqqâra. As many as two to three garlic cultivars were known at the time of Pliny the Elder (23-79 A.D.), the Roman naturalist.

Pliny extolled the virtues of garlic in his *Natural History*. "Garlic has powerful properties, and is of great benefit against changes of water and of residence . . ." Pliny says that garlic is an antidote for the poisonous bite of the shrew, dogbites, snakebites; it neutralizes the poisonous plants aconite and henbane. He recommends its use in the

treatment of asthma, as a cough suppressant, and to expel intestinal parasites. It is an anodyne (pain killer) for toothache—as a decocted rinse, crushed and inserted directly into a hollow tooth, or macerated with vinegar. When pounded with fresh coriander and taken in neat wine, Pliny says garlic acts as an aphrodisiac. However, according to Pliny, there are some drawbacks, which include dulling the sight, causing flatulence, injuring the stomach if taken in excess, and causing thirst (Jones, 1964).

In China garlic is known as *Da-suan*, and medicinal use is first recorded in Tao Hong-jing's *Ming Yi Bei Lu (Miscellaneous Records of Famous Physicians)*, published during the era of the North and South Dynasties, around 510 A.D. Garlic is known to have been cultivated in China as early as the Tang Dynasty (618-907). More commonly used today as a folk remedy rather than a drug in Traditional Chinese Medicine, primary uses in China include controlling dysentery, and as an antiparasitic, detoxicant, antifebrile, and stomachic (C.H. Yueh personal communication, 1987; H.Y. Hsu *et al.*, 1986).

Modern Usage

No other herb has served as many culinary and medicinal roles in as many cultures as garlic. Traditionally, the fresh cloves, garlic tea, syrup, tincture, and other preparations have been used as an aphrodisiac; to treat colds, fever, flu symptoms, coughs, earache, bronchitis, shortness of breath, sinus congestion, headache, stomach ache, high blood pressure, atherosclerosis, hypertension, diarrhea, dysentery, gout, rheumatism, whooping cough, pinworms, old ulcers, and snakebites; and for numerous other ailments, conditions, and applications (Foster and Duke, 1990).

Dozens of compounds have been indentified from garlic and its volatile oil including 33 sulfur compounds, 17 amino acids, germanium, calcium, copper, iron, potassium, magnesium, selenium, zinc, vitamins A, B₁, and C (Abdullah *et al.*, 1988). The main components of the volatile oil are sulfur compounds, especially allicin, diallyl disulfide, and diallyl trisulfide. These compounds are considered to be the primary active components of garlic (Leung & Foster, 1996). Other compounds, such as ajoene (formed by the combining of allicin and diallyl disulfide) have also been shown to have anti-platelet aggregation and antibiotic activity. A number of additional compounds have also been shown to contribute to the anti-platelet aggregation, cholesterol lowering, blood sugar regulating, and fibrinolytic activity of garlic (Kleijnen, Knipschild and Terriet, 1989). A study by chemists at the University of Qatar provides evidence for the occurrence of prostaglandins from a homogenized garlic extract (Al-Nagdy, Abdel-Rahman and Heiba, 1988).

Allicin is a by-product (produced by crushing or bruising the bulb) in which an odorless, sulfur-containing amino acid called alliin comes into contact with the enzyme allinase, resulting in conversion to allicin. Allicin itself is strongly antibacterial and is the primary component responsible for the typical potent garlic odor. Allicin is unstable and breaks down into diallyl-disulfide upon steam distillation for essential oil production (Tyler, 1993).

Recent interest has focused on the potential and use of garlic for the treatment of high blood pressure, atherosclerosis, hypoglycemia, digestive ailments, colds, flu, bronchitis, plus its antibacterial, antifungal, serum cholesterol-lowering and anti-thrombotic activity (Tyler 1993; Leung & Foster, 1996). Other activities which have been the subject of

research, primarily in developing countries, include the use of garlic to treat amoebic dysentery and epilepsy, plus anti-inflammatory, anti-fertility (oxytocic), anti-tubercular, and anti-toxic activity for the treatment of poisoning, such as industrial lead poisoning. Garlic has also been used as an adjunct therapy in the treatment of leprosy, significantly altering the bacteria index, while improving the clinical picture of the patients (Chadha, ed., 1985). A study by Joshi *et al.* (1987) indicated that garlic oil may act as a potent relaxant of the smooth muscle of the gastrointestinal tract, and should be further studied in patients with hypermotile intestinal disorders (as in diarrhea).

Antibacterial activity was first recognized in an 1858 study by Louis Pasteur. Various studies have shown that garlic extracts or various components have a broad spectrum antibacterial action against Gram-positive and Gram-negative bacteria. Alliin is considered to be the primary antibacterial component (Fulder, 1988). A 1984 study by Singh and Shukla demonstrated that garlic shows promising activity against eight out of nine clinical strains of bacteria which are highly resistant to antibiotics, suggesting the need for further research on the potential application of garlic against resistant bacteria.

Over 2,000 papers on the various aspects of the chemistry, pharmacology, and clinical applications of the genus *Allium* have been published in the past 20 years. These are reviewed by Koch & Lawson (1996).

Kendler (1987), in a review article on the relationship of garlic (and onion) to cardiovascular disease, notes that human *in vivo* publications on the use of garlic may have defects based upon problems associated with conducting controlled double-blind studies given the difficulties in masking garlic's characteristic odor. Marked differences in experimental conditions are cited as difficulties in making direct comparisons of studies. Use of various dosage forms and formulations including: fresh garlic, dried garlic, powdered garlic, freeze-dried garlic, essential oil of garlic, and various proprietary preparations in studies also make it difficult to compare results. Therefore, results should be interpreted with appropriate caution and attention to detail. Kendler concludes, however, that despite various methodological problems with garlic studies, with few exceptions, the same overall conclusions in human studies are reached. These studies are also supported by well-controlled animal studies. Given the fact that nearly seven hundred million Americans die from coronary heart disease each year (almost as many deaths as from all other causes combined), research on garlic should be given high priority. Other review articles on the effects of garlic in cardiovascular disease include those by Ernst (1987) and Fulder (1989).

Subjects relative to cardiovascular disease that have been studied include the blood pressure-lowering effect of garlic in hypertension, effect on platelet aggregation, fibrinolytic activity, and effects in hyperlipidemia (including lowering of serum triglyceride and cholesterol levels). The anti-thrombotic activity, given the anti-platelet aggregation or "blood thinning" properties, and fibrinolytic activity of garlic may be key areas to explore rather than other risk factors (Kendler, 1987).

Fibrinolysis (the dissolving of blood clots resulting from the degradation of fibrin) physiologically balances blood coagulation. When fibrinolytic activity becomes impaired, it may lead to a predisposition to blood clotting and thrombosis. Conversely, enhancement of fibrinolytic activity may protect against thrombosis, or myocardial or

cerebral infarction. Studies on garlic's fibrinolytic activity as it relates to heart disease are reviewed by Ernst (1987).

Block *et al.* (1984) characterized a compound from fresh garlic (termed ajoene) that was found to be the most active component with anti-thrombotic activity (preventing blood platelet aggregation or clotting of blood). Block (1986), citing unpublished studies by Catalfamo of the New York State Department of Health, along with research groups from the University of Delaware and Venezuela, states that ajoene's anti-thrombotic activity is the result of inhibiting exposure of fibrinogen receptors on platelet membranes. Block also notes that while other components of garlic oil (diallyl disulfide and methyl allyl trisulfide) have been claimed to be the active anti-thrombotic components, other workers have found them to be virtually inactive anti-thrombotic components. Attempts are underway to develop ajoene-containing products that will produce anti-thrombotic activity free from the odiferous antisocial side effects of the fresh bulbs (Block, 1986). As an anti-clotting agent, ajoene is at least as potent as aspirin. The platelet aggregation-inhibiting activity may be responsible for the potential utility of garlic as a useful protective agent in atherosclerosis, coronary thrombosis and stroke (Tyler, 1993).

Various studies have focused on the ability of garlic to reduce cholesterol, triglycerides, and increases high-density lipoprotein in the blood. A 1973 study by A. Bordia and H.C. Bansal demonstrated that garlic essential oil reduced serum cholesterol three hours after healthy volunteers ate fatty meals with garlic. Studies by Jain (1977) and Bordia (1981) demonstrated that decreases in serum cholesterol and triglyceride levels in normal and hyperlipidemic patients could be achieved with long-term daily ingestion of garlic. A study by Nitiyanant *et al.* (1987), and the 1981 Bordia study both showed initial rises in serum cholesterol levels, followed by declines after long-term administration (over five months). Unrestricted diets were involved in the studies. The Nitiyanant study also showed an increase in high density lipoprotein in the blood. Further studies are reviewed by Lau *et al.* (1983), Ernst (1987) and Lau (1988).

A meta-analysis of garlic clinical studies (Warchafsky *et al.*, 1993), reviewed 28 human studies on the effect of garlic on total serum cholesterol levels. Five studies met the evaluation criteria established by the authors, which, among other factors, included more than 75 percent of participants with initial cholesterol readings exceeding 200 mg/dl. They concluded that between one-half to one clove of garlic per day or an equivalent dietary supplement form reduced cholesterol levels by a conservative average of 9 percent.

A more recent review by H. D. Reuter (1995) analyzed 28 clinical studies on garlic based on design, test method, number of patients, duration of treatment, types of garlic consumed and dosage. Studies involved healthy patients, those with high levels of fats in the blood, patients with high cholesterol, as well as those suffering from hypertension, coronary heart disease, clogged arteries, and other conditions. Blood lipid measurements included a decrease in total cholesterol, increase of high density lipoproteins, inhibition of low density lipoproteins, and decreases in triglycerides. When averaged together, the patients in the studies had a 10.3 percent decrease in cholesterol levels and a 14.3 percent decrease in triglycerides. He suggested that significant cholesterol or blood lipid-lowering effect can be achieved with a daily dose of 600-900 mg of garlic powder, containing 3.6 to 5.4 mg of allicin.

Abdullah, Kirkpatrick and Carter (1989) reported on the results of a pilot study in which ten AIDS patients were given garlic extracts for a period of ten weeks. The activity of natural killer-cells and helper/suppressor ratios were measured. Six of seven patients were found to have normal natural killer-cell activity after six weeks of taking the extract as a food supplement. Natural killer-cell activity was abnormal at the beginning of the study. Four out of seven evaluable patients had an improved helper/suppressor ratio. The authors reported an improvement of AIDS-related conditions including diarrhea, genital herpes, candidiasis and pansinusitis with recurrent fever. An undefined "aged processed garlic extract" was used in the study. Given the size of the trial the results are statistically insignificant, but the preliminary results point to the need for further studies.

The German government's Commission E approves the use of garlic as a non-prescription medicine to lower cholesterol and to reduce other cardiovascular risk factors (Blumenthal *et al.*, 1996).

Summary

Garlic, used as food and medicine throughout the world, has a history of use predating the written word. Garlic supplies are abundant, the herb is inexpensive, and is generally recognized as safe. Consequently garlic has been the subject of intensive scientific research over the past five decades, resulting in over 2,000 scientific publications, which have shown antibacterial, antifungal, antitumor, hypoglycemic, hypolipidemic, and anti-atherosclerotic activity. These effects have been demonstrated in both animals and humans, though there is a need for more well-designed double-blind clinical trials to better determine therapeutic value, dosage levels, duration of treatments, and other parameters. Whatever the results of future research, garlic will likely remain as popular in the future as it has been for the past 5,000 years.

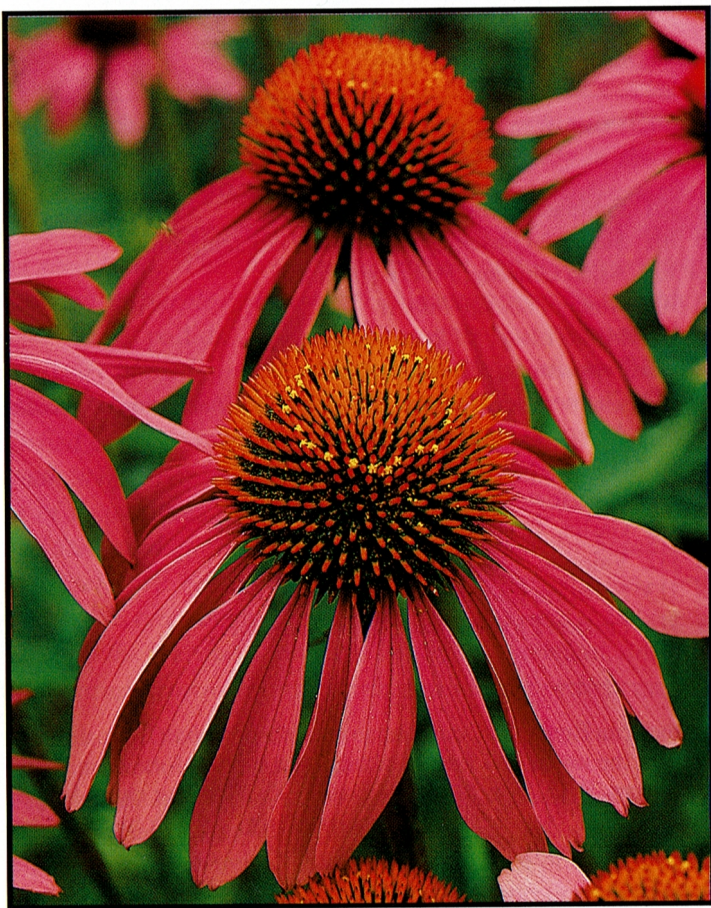
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Echinacea

The Purple Coneflowers



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On the cover:

Echinacea, *Echinacea purpurea*. Photo ©1996 Steven Foster.

Echinacea

The Purple Coneflowers

by Steven Foster

The genus Echinacea, a member of the sunflower family (Compositae or Asteraceae), has nine species found exclusively in the U.S. and Canada (McGregor 1968). The genus name is derived from the Greek echinos (hedgehog or sea urchin), referring to the prickly scales of the dried seed head. The three most common and widespread species, narrow-leaved purple coneflower (Echinacea angustifolia), pale purple coneflower (E. pallida) and purple coneflower (E. purpurea), have a long history of medicinal use, both in the United States and Europe. Ironically, over the past 50 years, most of the scientific studies published on this North American plant group are to be found in the German literature. Most studies have focused on aboveground, fresh parts of E. purpurea and, to a lesser extent, E. angustifolia. In the United States traditional use of echinacea, both in the botanical trade and the literature, has primarily focused on E. angustifolia. However, E. pallida has often been sold as E. angustifolia, and the two are often confused in the literature. Modern botanical, chemical, and pharmacological studies provide clear distinctions between these two species.

Botany

Four species, *E. atrorubens*, *E. paradoxa*, *E. sanguinea*, and *E. simulata*, have relatively narrow ranges. They have seldom been used, though botanists have documented the unwitting commercial harvest of at least three of those species from wild habitats. The Tennessee coneflower, *E. tennesseensis*, occurring in only five natural populations in central Tennessee, was one of the first plants to be awarded federal endangered species status (USDI/FWS 1979). In 1992 one of the largest populations of the Tennessee coneflower, in the 43-acre Couchville Cedar Glade, was purchased by Nature Conservancy. The purchase was made possible by a \$200,000 donation from the employees of American Airlines, through an aluminum can recycling program on the airline's planes. The rarest echinacea species is *E. laevigata* (smooth coneflower), an Appalachian native represented by just 6,000 individuals in 19 populations in four

states—only two percent as many plants as *E. tennesseensis*. It was afforded federal endangered species status as of November 9, 1992 (USDI/FWS, 1992).

History of Use

Medicinal uses of *Echinacea* species among American Indians, especially Plains groups and native groups of adjacent regions, were many and varied. In his classic, *Uses of Plants by Indians of the Missouri River Region*, anthropologist Melvin Gilmore (1919, p. 104) wrote of *E. angustifolia*, “This plant was universally used as an antidote for snakebite and other venomous bites and stings and poisonous conditions. *Echinacea* seems to have been used as a remedy for more ailments than any other plant.”

Mention of the medicinal uses of *Echinacea purpurea* comes early in the literature. In one of the first scientific works on American medicinal plants, Schöpf (1787), citing Clayton, mentions the use of *E. purpurea* for treating ulcers on a horses’s back caused by saddles. Clayton’s notes, to which Schöpf referred, were published in the second edition of *Flora Virginicus* (1762) by Laurens Theodore Gronovius (Foster, 1991). Subsequently, the plant was largely neglected until noticed by John King and R.S. Newton (1852) in the first edition of the *Eclectic Dispensatory*.

It was John King (1887) who introduced *E. angustifolia* to the medical profession. John Uri Lloyd (1921) gives a fascinating, detailed account of the history of the introduction of echinacea to pharmacy in his “Treatise on Echinacea.”

The European history of the introduction and use of *Echinacea purpurea* in many ways parallels its history in the U.S. In the first issue of William Curtis’s *Botanical Magazine* (1787), the plant is depicted as Plate Number 2 (C. Grey-Wilson, 1987). By 1895 echinacea products for homeopathic physicians had become available in Germany. Over the next 30 years the demand increased, while shortages were prevalent in Europe. Subsequently, in the late 1930s, commercial cultivation of *E. purpurea* began in Germany, introducing echinacea products to a wide European audience for the first time (Bauer & Wagner, 1988). The majority of pharmacological and clinical studies conducted since 1939 have involved *E. purpurea* preparations made from the fresh expressed juice of the flowering plant (primarily Echinacin®, Madaus AG, Cologne, Germany). Product forms include an ointment, a liquid form for external use, and an extract for internal use, as well as ampoules for intravenous and intramuscular injection. According to Bauer and Wagner (1991), over 280 echinacea pharmaceutical products are now available in Europe.

Current Usage

Much of the research has focused on the use of echinacea as a non-specific stimulant to the immune defense system. Over the past 50 years hundreds of studies have been published, primarily in the German literature, on the chemistry, pharmacology, and clinical applications of echinacea (Bauer & Wagner 1988, 1991).

The first study that led to significant investigations on the immune system parameters of echinacea was by Victor von Unruh of New York City (1916). Since 1955, many studies have appeared in the German literature dealing with the pharmacology of echinacea, as well as with the mechanisms and parameters of echinacea as a non-specific stimulant to the immune system. These studies began with several experiments conducted

on the local influence of cell resistance to disease, especially for the treatment of wounds (Bauer & Wagner 1988, 1991).

Most of the 350 scientific studies on the pharmacology and clinical uses of echinacea are included in Christopher Hobbs's excellent reviews (1989, 1993), to which the reader is referred. Main claims for pharmacological activity of echinacea (internally) include an increase in granulocytes in the blood, increase of phagocytic performance by granulocytes and macrophages, inhibition of virus production, activation of cytokins, such as interleukin 1, an increase of T-lymphocytes, and a shifting of the T4/T8-cell ratio in favor of T4 cells (Schöneberger, 1992).

Hobbs (1989, 1993), Bauer and Wagner (1991), and Awang and Kindack (1991) note that most of the clinical studies conducted in the past 50 years have involved injectable ampoules, a salve, or, to a lesser extent, oral dosage forms made from a proprietary preparation of *E. purpurea* fresh expressed juice of the flowering plant, preserved in 22% alcohol (Echinacin[®] made by Madaus AG, Cologne). According to Coeugnet and Kühnast (1986), oral preparations work as well as injectables, but act more slowly. Injectable forms are unavailable in the U.S. Internally, oral and injectable dosage forms available in Europe are generally used to strengthen natural immune defenses by enhancing properdin (a serum protein which under certain conditions can neutralize bacteria and viruses), and by stimulating the adrenal cortex. Externally, echinacea preparations indirectly have an anti-infective action by inhibiting hyaluronidase (an enzyme involved in the infection process by altering hyaluronic acid which has a cellular protective effect), stimulating new tissue production by increasing fibroblasts, and stimulating both blood and tissue-produced phagocytosis (scavenging of particles by specialized cells) (Hobbs, 1989; 1993).

Today preparations of echinacea are used for the external treatment of wounds, eczema, burns, psoriasis, herpes simplex, and other conditions. The preparations have been used internally as a preventative at the onset of cold and flu symptoms, and for *Candida* infections, chronic respiratory infections, prostatitis, polyarthritis (rheumatoid arthritis), and other diseases or ailments. Further studies have suggested that echinacea could play a therapeutic role in a wide range of clinical disciplines including dermatology, pediatrics, gynecology, surgery, urology, and the treatment of allergies (Hahn and Mayer, 1984). These indications are primarily ascribed to fresh aboveground preparations of *Echinacea purpurea* and the roots of *E. angustifolia* and *E. pallida* (Hobbs, 1989; 1993, Bauer & Wagner, 1991; Foster, 1991).

Many chemical components have been identified from echinacea species. However, according to R. Bauer and H. Wagner (1988, 1991), it is not possible at this time to attribute the effects of echinacea preparations to a specific substance. The most important constituents to which activity can be attributed include the volatile oil, caffeic acid derivatives, polysaccharides, polyines, polyenes, and isobutylamides (responsible for the "tingling" or "numbing" sensation produced on the tongue, especially by *E. angustifolia* root which has highest concentrations of this chemical group). Bauer, Wagner, and co-workers have shown that these compounds occur in varying concentrations, depending upon the species, plant part, and other factors.

Problems with the identity of various echinacea species, and the presence of substitutes, especially *Parthenium integrifolium*, have been recognized in commercial

echinacea products (Foster 1985a, 1985b, 1991; Bauer & Foster, 1989). Researchers believe this emphasizes the need for proper identification of echinacea species used in commercial products (Bauer & Wagner, 1987, 1988, 1991; Bauer, Kahn & Wagner, 1987).

Recent clinical studies have focused on the optimum time and dosage for use of echinacea preparations in the treatment of prevention of cold and flu symptoms. Braünig *et al.* (1992) in a double-blind placebo-controlled study with 180 volunteers studied the effect of an *E. purpurea* root ethanol extract (1:5 in 55% ethanol) in relieving the symptoms and duration of flu-like symptoms. Compared with the placebo control group, volunteers who received 900 mg/dose (equivalent to about 4 droppers full) exhibited statistically significant improvement compared with the placebo. Volunteers who received half that dose (450 mg/dose) showed improvement only comparable to the placebo. The study highlights the importance of dosage in expected effectiveness of echinacea preparations.

Another recent double-blind, mono-centric, placebo-controlled clinical study examined the immunostimulating influence of an expressed fresh juice *E. purpurea* preparation on the course and severity of colds and flu-like symptoms with patients deemed to have greater susceptibility to infections (as predetermined by T-cell ratios in the blood). A total of 108 patients (54 control; 54 treatment) were evaluated over an eight-week period. They received a dose of 2-4 ml/day. Compared with the placebo group, the treatment group had a decrease in frequency of infections, an increase in length of interval between infections, a reduction in the average duration of colds, and less severe symptoms. The study shows that patients with diminished immune response (expressed by a low T4/T8 cell ratio), could benefit from preventative treatment to cold and flu infections with the echinacea preparation (Schöneberger, 1992).

A recent review (Melchart *et al.*, 1994) assessed 26 controlled clinical studies (18 randomized, 11 double-blind) on echinacea in immunodulation. Six of the studies involved three different echinacea extracts, while 20 involved combination products (containing other ingredients). The methodology quality of most of the studies was scored as low. However, the existing studies did show that Echinacea preparations can be effective immunomodulators. Further research must identify best preparation methods and dose for specific indications.

The risk-benefit ratio of the fresh squeezed juice of *Echinacea purpurea* was recently analyzed in a retrospective review (Parnham, 1996). Only studies providing information on dose and route of administration, in addition to well-defined patient populations were included. A number of side effects have been observed with parenteral (injectable) preparations in Germany including shivering, fever, and muscle weakness. This effect is related to the migration of activated T-helper cells to target organs. These symptoms are not observed in oral administration of the echinacea preparation. The expressed juice of fresh-flowering *E. purpurea*, when taken orally for up to 12 weeks, produced no adverse reactions (other than patient-reported dislike of the taste) for a wide range of patients, from infants to the adults. The author concludes that the expressed juice of *E. purpurea* can be considered a safe product for long-term oral immunostimulation, but that more research is needed to assess effectiveness.

The Commission E of the German Institute for Drugs and Medical Devices

approves several echinacea preparations for use in colds, flus, and infections of the upper respiratory tract (Blumenthal, *et al.*, 1996).

While hundreds of studies have been published on echinacea and its medicinal value, further studies are still needed to develop standards of identity; correct form, amount, and timing of dosage; and differences in various preparations of echinacea (Bauer & Wagner, 1988). To date, pharmacological investigations have proven that echinacea extracts do have a positive influence on the immune system, and we are now beginning to better understand how echinacea can be used with optimum benefit for the prevention and treatment of minor ailments.

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Siberian Ginseng

Eleutherococcus senticosus



Steven Foster

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On the cover:

Siberian ginseng, *Eleutherococcus senticosus*. Photo ©1996 Steven Foster.

SIBERIAN GINSENG

Eleutherococcus senticosus

by Steven Foster

Russian research conducted over the past 30 years and its long history of use in China have catapulted a shrubby member of the ginseng family (Araliaceae), Siberian ginseng or eleuthero, into international prominence as an adaptogen as well as a non-specific immunostimulant.

Introduction

Botanists know the plant as *Eleutherococcus senticosus* (Rupr. and Maxim.) Maxim. The plant was formerly known as *Acanthopanax senticosus*, a name still widely used by Chinese scientists. Soejarto and Farnsworth (1978) and Shiu Ying Hu (1980) both published on the taxonomic position and scientific name of this plant, concluding that *Eleutherococcus senticosus* is the earliest validly published name, and therefore the name that should be used.

Distribution

Eleuthero is a spiny-stemmed shrub with numerous stalks arising from the root, growing to a height of 9 feet in 7-10 years. It is found in northeast Asia, including much of the far southeastern Russia, northeast China, adjacent Korea, and Japan. In China it is indigenous to Heilongjiang, Jilin, Liaoning, Nei Mongol, south to Hebei and Shanxi (the six most northeasterly provinces of China). The major production region is in what was formerly known as Manchuria, now composed of the Chinese provinces Heilongjiang, Jilin, and Liaoning. According to Halstead and Hood (1984) it is most abundant in China in the Xiaoxinganling Mountains of Heilongjiang, the most northeastern province. In Japan the shrub occurs spontaneously on the northern island of Hokkaido (Ohwi, 1965).

In Russia, the plant's distribution includes most of the eastern maritime regions, extending to the Middle Amur region in the north to Sakhalin, and is most abundant in the Khabarovsk and Primorsk districts, covering some 10 million hectares (Farnsworth *et al.*, 1985). A. I. Poyarkova (1973) reports it occurs in mixed and coniferous mountain forests, at forest edges, and produces groups in thickets or small undergrowths. It is a common plant of undergrowths, and is rarely found in oak groves at the foot of cliffs and ravines. It is more rare in high riparian woodland. Halstead and Hood (1984) state that botanist O.D. Forsh found as many as 10,000 sprouts per hectare (2 1/2 acres), and that the plant grows so thickly in some areas that it forms almost impenetrable thickets.

In the United States it has historically been grown as a specimen plant at botanical gardens and arboreta, including Harvard University's Arnold Arboretum (introduced from Leningrad in 1892) and the National Arboretum in Washington, D.C. In recent years seeds have become available in North America, and experimental plots have reportedly been established in Montana, Oregon, and other states.

Taxonomy

According to N.R. Farnsworth *et al.* (1985), common names for the plant include “Siberian ginseng,” “touch-me-not,” “devil’s shrub,” “eleutherococc,” “spiny eleutherococc,” “wild pepper,” “eleuthero,” “eleuthero ginseng,” and “devil’s bush.” A.I. Baranov (1979) proposed the common name, “Ussurian thorny pepperbush,” and further argued that “Siberian Ginseng” was a misnomer because it did not comply with either phytotaxonomical or phytogeographical characteristics of the plant. In the late 1970s and early 1980s there was considerable debate in the herb industry as to the name under which the plant should be traded in the U.S. All arguments aside, the names “Siberian ginseng,” “eleuthero-ginseng,” and “eleuthero” have become well established in both the herb trade, as well as the scientific and popular literature. Furthermore, *Eleutherococcus senticosus* is clearly established as the correct botanical name of the plant. We will refer to the plant as eleuthero (*Eleutherococcus senticosus*), the name adopted in the American Herb Products Association’s *Herbs of Commerce* publication (Foster, 1992).

In Chinese tradition, the whole root and rhizome is known as “*Ci-wu-jia*.” *Jia-pi*, the bark of *E. gracilistylus* (*Acanthopanax gracilistylus*) is the official source of *Wu-jia-pi* in the Chinese Pharmacopoeia. The bark of *E. senticosus* (*Jia-Pi* or *Ci-Wu-Jia-Pi*) is sometimes used as a substitute. *Ci-wu-jia*, the root of *E. senticosus*, is a separate article of materia medica in Chinese tradition. An unrelated plant, *Periploca sepium*, a viney member of the milkweed family (Asclepidaceae), is known in Traditional Chinese Medicine as “*Wu-jia*” (Foster and Yue, 1992) or “*Xiang-jia-pi*” (bark); “*Gang-liu-pi*” (bark), and “*Bei-wu-jia-pi*” (bark) (S.Y. Hu 1980b). Similarities of the Traditional Chinese names for *Eleutherococcus senticosus* and *Periploca sepium* have prompted confusion and the latter has entered the American herb trade and been sold as *E. senticosus*.

A letter to the editor in the 12 December 1990 issue of the *Journal of the American Medical Association* (Koren, *et al.*, 1990) reported on a purported case of neonatal androgenization associated with maternal “ginseng” use in Canada — the so-called “hairy baby” case. The isolated case was attributed to the mother’s use of “pure Siberian ginseng.” The authors erroneously confused eleuthero with *Panax ginseng* in their discussion. Further follow-up research by D. V. C. Awang (Natural Products Section, Bureau of Drug Research, Health and Welfare Canada), pointed out the egregious errors in the report by Koren and coworkers and revealed that the product in question in fact did not contain eleuthero, but instead contained *Periploca sepium* (Awang, 1991a, 1991b). Waller *et al.* (1992) performed pharmacological tests on rats with the implicated plant material, and observed no androgenicity, and concluded, “the effects observed were specific to humans and possibly related to an undetermined peculiarity of the subject patient.” This case highlights the need for proper botanical identification of herbal products and further alerted the herb industry to this potential adulteration problem, prompting new testing procedures.

Chinese products of *E. senticosus* entered the American herb market in the late 1970s as “Wuchaseng” and “Wujiaseng.” There appears to be no historical precedent in Chinese traditions to applying the qualifier “seng” to *E. senticosus* (S.Y. Hu, 1979). “Seng” refers to fleshy rootstocks used in Chinese medicine as tonics. “Gin-seng,” for example is one “seng”-producing plant. As *E. senticosus* has a woody root, it is not a “seng” by traditional Chinese definitions.

“*Radix Acanthopanax senticosi*,” *Ci-wu-jia* (as *Acanthopanax senticosus* (Rupr. et Maxim.) Harms), is listed as an official article of materia medica in the 1985 edition of the *Pharmacopoeia of the People's Republic of China*. It is first mentioned in the Chinese literature in the 2,000-year-old classic *Shen Nong Ben Cao Jing* (the *Divine Husbandman's Classic of the Materia Medica*). In this work, Shen Nong lists 365 herbs in three classes (based on importance of use). *E. senticosus* is placed in the first class (Foster and Yue, 1992).

Traditional & Modern Uses

The Chinese herbal medicine “*Ci-wu-jia*” was, as previously stated, first mentioned in *Shen Nong Ben Cao Jing*. However, because of word-origin problems in relation to the exact source plant referred to in ancient texts, there is considerable confusion over the exact historical beginnings of the use of *E. senticosus* in China. These problems are reviewed by Halstead and Hood (1984). It is only in the last 25 years that Chinese researchers have taken an active interest in the plant because of the similarity of its properties to those of ginseng. Indications in Traditional Chinese Medicine for use of *E. senticosus* include benefiting “*qi*” (vital energy), treating deficiency of “*yang*” in the spleen and kidney, and normalizing body functions (Foster and Yue, 1992).

Duke and Ayensu (1985) report that the plant is used in the northeastern city of Harbin, China as a folk remedy for bronchitis, heart ailments, and rheumatism. Citing representatives from the China National Native Produce Corporation, Duke and Ayensu also report that the Chinese believe regular use of the plant helps to restore vigor, improve general health, restore memory, promote good appetite and increase longevity, basically serving as a preventative medicine and general tonic.

Russian Research

Research on *E. senticosus* in the Soviet Union began as the result of a screening program of far eastern members of the ginseng family (Araliaceae) after Soviet researchers had become convinced of the potential value of *Panax ginseng* as an adaptogen (S. Fulder, 1980). Early pharmacological results, published in 1958, prompted the Pharmacological Committee of the U.S.S.R. Ministry of Health to authorize preliminary clinical tests on *E. senticosus* in 1959. An article by I. I. Brekhman, widely regarded as the leading researcher on *E. senticosus*, was published in 1960. A symposium on plants of the ginseng family was held in Leningrad in June of 1961, resulting in the publication of an 86-page collection of proceedings. The following year, *Eleutherococcus* was approved for human use by the Soviet government's Ministry of Health (Halstead and Hood, 1984).

At first described as a “stimulant” and “tonic,” by 1958 the term “adaptogen” was applied by Soviet researchers to describe the action of *Eleutherococcus*. The term “adaptogen” was coined in 1947 by N.V. Lazarev to refer to a substance which was claimed to increase “non-specific” resistance of adverse influences to an organism (Farnsworth *et al.*, 1985). Farnsworth *et al.* (1985) described Brekhman's definition of an adaptogen as:

- 1. A substance which “must be innocuous and cause minimal disorders in the physiological functions of an organism.”
- 2. A substance which “must have a nonspecific action,” such as the ability of *E. senticosus* extracts to modulate stress and improve performance under a wide variety of stressful conditions.

- 3. A substance which “usually has a normalizing action irrespective of the direction of the pathologic state.”

Since the early 1960s clinical studies involving more than 2,100 normal and stressed human subjects have been conducted in Russia using an orally administered 33% ethanol root extract of *E. senticosus*. Doses ranging from 2 to 16 ml are taken one to three times a day for up to 60 consecutive days (with a two-to-three-week resting interval between courses of administration). Up to five courses of administration have been given to male and female subjects, ranging from 19 to 72 years of age (Farnsworth *et al.*, 1985). These Soviet studies are summarized in English in the 1985 review article by Farnsworth *et al.* The studies were performed to measure the adaptogenic response of humans to adverse conditions such as heat, noise, motion, work load increase, exercise, as well as to measure improvements in auditory disturbances, increased mental alertness, work output and the quality of work both under stress-inducing conditions and in athletic performance (Farnsworth *et al.*, 1985).

Following successful conclusion of these studies, which showed positive results and virtually no adverse side effects, the extract of *E. senticosus* is widely used by the Soviet public, taken by deep sea divers, mine and mountain rescue workers, explorers, soldiers, factory workers, cosmonauts and athletes in Russia (Fulder, 1980).

Additional studies on its clinical effectiveness and side effects have been conducted involving over 2,200 human subjects suffering from a wide variety of ailments including neuroses, atherosclerosis, several forms of diabetes, hypertension, hypotension, chronic bronchitis, cancers, acute head trauma, rheumatic heart disease and other ailments. Dosage reported in these studies was less than for healthy subjects, ranging from 0.5 ml to 6.0 ml one to three times per day, with courses of administration lasting for a shorter overall duration of 35 days. Again, administration was interrupted for two to three weeks between treatments. These studies showed measurable improvements or, in some cases, normalization with few side effects, though in no way can the results be interpreted as “cures” for the ailments under investigation. These studies are summarized by Farnsworth *et al.*, 1985.

Extensively researched over the last 30 years, and with a 2,000-year-old history of use in China, eleuthero is emerging as one of the best documented “new” medicinal plants of the late twentieth century. Over 35 compounds have been identified from the roots of *E. senticosus* (Farnsworth *et al.*, 1985). One group of compounds, the eleutherosides, has been shown to be primarily responsible for the plant’s adaptogenic activity. In addition, according to Wagner and Proksch (1985), two polysaccharides in the root have been shown to display immunopotentiating activity (in phagocytosis), and immunoadjuvant activity (in B lymphocytes). However, the polysaccharides may precipitate out of alcohol extracts of the root.

Preparations of the root have been shown to be non-toxic when administered over a long period of time. Siberian ginseng products are used by millions of Soviet citizens both to improve and increase the quality and quantity of physical and mental work, while helping the body “adapt” to stressful conditions. Plant preparations are also known to help increase non-specific resistance against a number of pathogens, as well as certain physical and chemical factors (Lucas, 1973). Currently, the German government allows eleuthero to be used similarly to *Panax ginseng* as a tonic for invigoration and fortification during

times of fatigue and debility; for declining work capacity and concentration, as well as during convalescence. (Blumenthal *et al.*, 1996).

The Future

In an interview with the eminent Soviet physician I. I. Brekhman, McCaleb (1988) reviewed problems with modern pharmacological research which attempts to evaluate a “magic bullet” treatment for a specific disease or disease organism, and the drawbacks of such an approach when attempting to evaluate medicines with a positive influence on the estimated 60-80 percent of people who find themselves in a state between optimum health and diagnosed illness. Scientific models for determining efficacy of “prophylaxis” or “staying near to health” are not well established.

Farnsworth *et al.* (1985) state that there is extensive evidence to support the adaptogenic nature of *E. senticosus* extract in both animal and human models, but that pharmacological explanations of the mechanism of action are poorly understood. They suggest that future models focusing on the biochemical effects of autacoids (such as prostaglandins) may reveal an as yet unknown mechanism that may be responsible for “adaptogenic” effects.

The study of “adaptogens” is in its infancy. Past and future work on *E. senticosus* could result in new ways of thinking about medicinal plants as well as new directions in research.

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Asian Ginseng

Panax ginseng



Steven Foster

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Botanical Series - 303

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On the cover:

Asian ginseng, *Panax ginseng*. Photo ©1996 Steven Foster.

ASIAN GINSENG

Panax ginseng

by Steven Foster

Ginseng, Panax ginseng C. A. Meyer, is the most famous of all Asian medicinal plants. Used in China for over 2,000 years, numerous scientific studies over the past 40 years have concentrated on the chemistry, pharmacology, and clinical aspects of ginseng use. Much of the research has provided a scientific basis for the traditional claims for ginseng use.

Origins

A member of the ginseng family (Araliaceae), the genus *Panax* contains about six species native to eastern Asia and two native to eastern North America. Confusion in taxonomic interpretation has resulted from use of *P. pseudoginseng* as a synonym for *Panax ginseng* (L. H. Bailey *et. al.*, 1976; Tyler, 1993). *Panax schin-seng* Nees is also a synonym for *Panax ginseng* (H. L. Li, 1942). The confusion may arise in part from the fact that T. F. L. Nees had, in 1833, expressly included the earlier and legitimate *P. pseudoginseng* under his *P. schin-seng*. According to S. A. Graham (1966), *P. schin-seng* was superfluous when published, thus illegitimate. The earliest legitimate botanical name is *P. ginseng*, first used by C.A. Meyer (1843). It is recognized as a distinct entity from *P. pseudo-ginseng* in recent Chinese taxonomic treatments on the genus *Panax*. Ho and Tseng (1978) recognize three Chinese species of *Panax* (*P. ginseng*, *P. pseudo-ginseng*, and *P. zingiberensis*). They list five varieties under *P. pseudo-ginseng*.

Panax derives from Greek roots, *pan* meaning "all," and *akos*, "cure," referring to the "cure all" or "panacea" attributes of the root's healthful virtues. "Ginseng," "jen-seng," "schin-seng," or "ren-shen" (various transliterations of the same Chinese ideograms), means "essence of the earth in the form of a man" (Graham, 1966). S.Y. Hu (1976) states that *sêng* is a term employed by Chinese medicinal root gatherers for fleshy roots used as tonics. *Sêng* is preceded by modifiers to denote the source material or medicinal property (such as "bitter seng," "black seng," "Mingtang seng," "prince seng"). All species of *Panax* do not produce *sêng* and all *sêng*-producing plants are not in the genus *Panax*. S.Y. Hu (1979) uses this metaphor, "A horse is a mammal, but not all mammals are horses. Likewise, ginseng is a *Seng* but not all sengs in Chinese medicine are ginseng." She documents 62 species of "seng-producing" plants in 40 genera of 20 botanical families.

History

According to S. Y. Hu (1977a), the earliest written account of ginseng is from *Shen Nong Ben Cao Jing*, attributed to the Divine Plowman Shen-Nong, compiled in the late Han Dynasty (approx. the first century A.D.). The short account of 44 words included the name ginseng, two synonyms, taste and property, habitat, and medicinal uses of ginseng (S. Y. Hu, 1977a). In her translation of the account, S. Y. Hu (1977a, p. 289) writes, "It is used for repairing the five viscera, quietening the spirit, curbing the emotion, stopping agitation, removing noxious influence, brightening the eyes, enlightening the mind and increasing the wisdom. Continuous use leads one to longevity with light weight."

In the 1596 classic of the Chinese materia medica Li Shi-zhen's *Ben Cao Gang Mu*, ginseng is listed in the superior class of herbs. Small amounts were said to develop light weight while improving vitality (S. Y. Hu, 1976).

The first description of the plant by a Westerner was provided by Père Jartoux, a Jesuit missionary stationed in Beijing. His observations, made in 1709, include uses, description, and habitat, plus historical and personal notes. In 1714 Jartoux's account was published in English.

"Nobody can imagine that the Chinese and Tartars would set so high a value on this root, if it did not constantly produce a good effect. Those that are in health often make use of it, to render themselves more vigorous and strong; and I am persuaded that it would prove an excellent medicine in the hands of any European who understands pharmacy, if he had but a sufficient quantity of it to make such trials as are necessary, to examine the nature of it chemically, and to apply it in a proper quantity, according to the nature of the disease for which it may be beneficial" (Jartoux, 1714).

Nearly three centuries after those words were written, European, Japanese, Chinese, Soviet, and, to a lesser extent, American researchers have examined the chemical nature of *Panax ginseng*, as well as its benefits, in dozens of chemical, pharmacological, and clinical studies.

According to the tenets of Traditional Chinese Medicine, the taste of *Panax ginseng* is sweet-bitter, and it has a warming character. It is a tonic used to increase strength, increase blood volume, promote life and appetite, quiet the spirit, and give wisdom. It is used alone or in prescriptions for general weakness, deficient qi (chi) patterns, anemia, lack of appetite, shortness of breath with spontaneous perspiration, nervous agitation, forgetfulness, thirst, and impotence (S. Y. Hu, 1976).

Current Usage

Pharmacological and clinical studies conducted over the past 40 years focus on radioprotective, antitumor, antiviral, and metabolic effects; antioxidant activities; nervous system and reproductive performance; effects on cholesterol and lipid metabolism, and endocrinological activity (Ng and Yeung, 1986; S. Shibata *et al.*, 1985).

Inconsistent results have been reported on interpretation of various studies attempting to prove a scientific basis for the activity of ginseng products (W. H. Lewis *et al.*, 1983; W. H. Lewis, 1986). However, S. Shibata *et al.* (1985) note that many of the inconsistencies are due mostly to different procedures in preparation, resulting in extractions lacking in biologically active components.

Popular and scientific reviews of ginseng research may be predisposed to either advocacy or skeptical negativity. Peer scrutiny, polarization of research methods, and

data interpretation, as evidenced by question and answer sessions at international ginseng symposia, are common in ginseng research (Proc. 1st-4th Int. Ginseng Symp. 1974-1984).

Studies by the Bulgarian researcher Petkov (1959, 1961, 1965, 1975; Petkov and D. Staneva-Stoicheva, 1963, 1965) provided a pharmacological basis for a stimulative effect of ginseng on the central nervous system, a hypotensive effect, respiratory stimulation effect, blood sugar lowering activity, an increase of reactivity of cerebrocortical cells in response to stress, increase of erythrocyte and hemoglobin counts, and blood cholesterol lowering effects.

I. I. Brekhman, the pioneer Soviet researcher on the pharmacology of East Asian ginseng family members, gave Soviet soldiers a ginseng extract or placebo, and found that those who had the ginseng ran faster in a 3 km race. In another experiment, radio operators receiving a ginseng extract made fewer mistakes and transmitted text faster than those who took a placebo. The results suggested that ginseng extracts improved stamina (ex. S. Shibata *et al.*, 1985). Brekhman attempted to confirm results of human trials with mice experiments, showing that mice given ginseng extract swam longer than controls, suggesting an antifatigue action. However, W. H. Lewis *et al.* (1983) showed no significant differences in stamina or longevity between mice ingesting infusions of *Panax ginseng* (and other species) compared with controls.

Ginseng contains a number of active constituents including saponins, essential oil, phytosterol, carbohydrates and sugars, organic acids, nitrogenous substances, amino acids and peptides, plus vitamins and minerals (Hou, 1977). At least 22 saponins, known as ginsenosides (or panaxosides) have been isolated and found to be the most active constituents (Hou, 1977). (See Hou, 1977; Shibata *et al.*, 1985; and Leung and Foster, 1996 for reviews of chemistry.)

A number of experiments by Saito *et al.* (1974a, 1974b) employed pure ginseng saponins to determine the effect of ginseng components on normal and exhausted mice to determine anti-fatigue activity and the effect on the central nervous system. Results were opposite with different chemical fractions. Central nervous system sedative, tranquilizing, and hypotensive actions were shown for the ginseng saponin known as ginsenoside R_b-1. CNS-stimulant, hypertensive, and antifatigue activity was shown for ginsenoside R_g-1. While a CNS-stimulant at lower doses, higher doses of ginsenoside R_g-1 had sedative action (Shibata *et al.*, 1985). The conflicting results of these studies are relative to type of preparation, route of administration, dosage, and presence or absence of biologically active compounds, among other factors.

Review of the pharmacological actions of pure ginseng saponins by S. Shibata *et al.* (1985) indicates that ginsenoside R_b-1 has CNS-depressant activity, is anticonvulsant, analgesic, antipyretic, antipsychotic, ulcer-protective, inhibits conditioned avoidance response, has weak anti-inflammatory activity, an antihaemolytic action, and increases gastrointestinal motility. In addition it accelerates glycolysis, and accelerates serum and liver cholesterol, nuclear RNA, and serum protein synthesis.

Ginsenoside R_g-1 has shown weak CNS-stimulant activity, anti-fatigue action, aggravation of stress ulcer, and a slight increase in motor activity. In behavioral tests it showed an acceleration of discrimination behavior in pole-climbing tests and Y-maze tests, a reversal learning response in the Y-maze test, and one-trial passive avoidance learning using the step-down method.

In experiments on embryonic cultures of animal nerve tissue, Saito (1980) found

that ginsenosides R_{b-1} and R_d potentiated nerve growth factor. Nerve growth factor is recognized as having an important role for the survival, regeneration, and regulation of catecholaminergic neurons of brain and ganglion in adult animals. While not providing definitive conclusions, the research suggested further mechanisms and research directions for determining possible pharmacological activity or applications of ginseng saponins.

Radioprotective studies involving the effects of ginseng extracts on X-ray irradiated rodents protected animals from the damaging effect of radiation. This dose-dependent effect included an increase in survival rate, prevention of hemorrhage, recovery of spleen weight and DNA content, and recovery of white and red blood cells and blood platelets. Both positive and negative results have been reported from various ginsenoside fractions under varying conditions (Ng and Yeung, 1986).

W. H. Lewis (1986) and Ng and Yueng (1986) report on various studies on antitumor activity (ether, alcohol, and water extracts) of *Panax ginseng*. Ether extracts showed weak positive activity *in vitro* on several types of cancer cells, while water, alcohol, and ether extracts showed negative results in other cancer cell types.

Antioxidants which decrease lipid peroxides associated with adult diseases, including liver and eye disease, atherosclerosis, and nerve aging, have been suggested as possible therapeutic agents in the development of geriatric drugs. Studies have shown that certain glycoside fractions of processed (red) *Panax ginseng* have antioxidant activity. In Traditional Chinese Medicine, decocting ginseng in iron vessels is contraindicated. Ng and Yeung (1986) report on a rational scientific explanation for this tradition in reviewing antioxidant experiments with ginseng.

Hypoglycemic activity has been shown for *Panax ginseng* extractions suggesting a preliminary scientific basis for the traditional use of ginseng in diabetes. While research results are promising, W. H. Lewis (1986) notes that much more research must be conducted before ginseng could be considered useful in the treatment of diabetes mellitus.

Clinical trials have focused on the effect of red ginseng powder on diabetics, excessive fat in the blood, performance and stress, postoperative gynecological patients, and abuse of ginseng products (Ng and Yeung, 1986; W. H. Lewis, 1986; S. Shibata *et al.*, 1985; S. Fulder, 1980). Seven European clinical studies involving extracts standardized to 4 percent and 7 percent of ginsenosides are reviewed by Ng and Yeung (1986). Results included a shortening of time to react to visual and auditory stimuli, increased respiratory quotient, increased alertness, power of concentration, grasp of abstract concepts, and increases in visual and motor coordination. While positive though conflicting results have been reported in a number of research parameters, most researchers agree that further clinical studies, especially those involving well-defined pure constituents or assays of chemical content of batch materials used in crude root preparations, are warranted.

Currently, the German government's Commission E allows *Panax ginseng* products containing at least 1.5 percent ginsenosides, calculated as ginsenoside R_{g-1} to be labeled for use as a tonic for invigoration and fortification during times of fatigue and debility; for declining work capacity and concentration, as well as during convalescence. Commission E notes that adverse reactions or contraindications are not known for normal ginseng use. (Blumenthal *et al.*, 1996).

Summary

Oriental ginseng, *Panax ginseng*, has more than a 2,000-year-old history of continuous

safe use without reports of clear, predictable side effects when taken in moderation. Shrouded in a mix of mystery and extravagant claims, numerous scientific studies over the past 40 years have begun to establish a chemical, pharmacological, and clinic basis for the traditional claims for this well-known, but little understood herb. Quoted in Blumenthal (1987), N.R. Farnsworth states, "Nothing is proven in pharmacology until different groups all publish and agree." To evaluate the existing scientific studies published in Russian, Japanese, Chinese, German, English, and other languages is a nearly impossible task, given the complexities of interpreting the data (Blumenthal, 1987). Though hundreds of studies have been conducted on ginseng, there is a need for long-term controlled studies in humans, perhaps using unconventional or novel models, that will help identify its benefits in a predictable and safe manner (Blumenthal, 1987). Farnsworth and Bederka (1973) note however, "The use of ginseng as a general body tonic would seem to be well founded."

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Ginkgo

Ginkgo biloba



Steven Foster

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On the cover:

Ginkgo, *Ginkgo biloba*. Photo © 1996 Steven Foster.

GINKGO

Ginkgo biloba

by Steven Foster

Historical Overview

Once common in North America and Europe, ginkgo became extinct over much of its range during the Ice Age, though surviving in China. Three hundred years ago, Englebert Kaempfer, a German surgeon employed by the Dutch East India Company, was the first Westerner to observe and describe the tree. He called it “ginkgo,” an eighteenth century phonetic pronunciation of a Japanese name. In 1771, Linnaeus gave it the binomial *Ginkgo biloba*. The tree was introduced to North America in 1784 in the garden of William Hamilton at Woodlands near Philadelphia (Li, 1956). Ginkgo is widely grown as an ornamental under adverse conditions such as inner city environs.

Over the past 20 years ginkgo has become an increasingly well-known medicinal plant worldwide. Its complex and unique chemistry gives it remarkable resistance to pests and disease, tolerance to adversity, and a storehouse of biologically active compounds. Ginkgo leaf extract, standardized to percentages of the known active constituents, is now among the best-selling phytomedicine in Europe.

The leaves, known as *Bai-guo-ye* in Traditional Chinese Medicine, have been used for “benefiting the brain,” as an astringent to the lungs, to relieve symptoms of asthma and cough, and in the treatment of filariasis (a chronic disease caused by a parasitic nematode) in doses of 4.5-9 g (Yueh, 1987). While mention of the tree itself came much earlier in Chinese literature, ginkgo leaf is first mentioned in Lan Mao’s *Dian Nan Ben Cao* (Pharmaceutical Natural History of Southern Yunnan), published in 1436 during the Ming dynasty. Lan Mao notes external use to treat skin and head sores as well as freckles. Internal use of the leaves is first noted in Liu Wen-Tai’s *Ben Cao Pin Hui Jing Yao* (Essentials of the Pharmacopoeia Ranked According to Nature and Efficacy), an imperial commissioned work recorded in 1505. Liu Wen Tai notes use of the leaves in the treatment of diarrhea (Leung, 1990). Clinical experience in modern China has focused on using tablets or injectable drug forms in the treatment of angina pectoris, chronic bronchitis, and its effect on lowering serum cholesterol levels (Yueh, 1989). An infusion of the boiled leaves is still used in the treatment of frostbite (Michel and Hosford, 1988).

Modern Use

Today ginkgo leaf extracts manufactured in Europe and Asia are used for a wide variety of conditions. Clinical use focuses on the treatment of poor circulation, heart disease, eye disease, ringing in the ear (tinnitus), chronic cerebral insufficiency, accidents involving brain trauma, dementia, and various conditions associated with senility (Drieu, 1985; Warburton, 1988).

Preparations currently available on the world market include dried leaf, tinctures,

homeopathic preparations, and various extracts. The leaves are a rich complex of chemical structures. Active constituents include bioflavonoids such as the flavonoid glycosides kaempferol, quercetin, and isorhamnetin; flavones; and organic acids. Novel diterpene lactones, unique to ginkgo, are currently the focus of intensive pharmacological and clinical research. These include the ginkgolides (A, B, C, and M) and bilobalide, a sesquiterpene (Boralle, Braquet, and Gottlieb, 1988).

According to Drieu (1985), the total extract from *Ginkgo biloba* is active, while single isolated components do not provide the activity of the total extract. This suggests a pharmacological synergism of components rather than a single biologically active compound. As far as we can ascertain, virtually all of the nearly 250 pharmacological and clinical studies published in the last 15 years have involved a specific standardized extract developed and researched in Germany. It is subject to a complex extraction process and standardized to 24 percent flavone glycosides, as well as being further calibrated for, among other constituents, ginkgolides and bilobalide. This specific extract is produced by a German/French consortium (Drieu, 1985, 1988).

The standardized extract of the leaves is beneficial in a broad range of physiological dysfunctions and pathological conditions, including those involved with circulation, blood conditions, metabolism, and immune function (Michel and Hosford, 1988). Pharmacological effects of the extract include free-radical scavenging properties as effective as uric acid, plus the ability to inactivate the formation of radicals not affected by uric acid. The extract inhibits lipid peroxidation of membranes, helping to maintain integrity and permeability of cell walls (Pincemail and Deby, 1988). Chatterjee (1985) reviewed studies showing that the ginkgo extract has vascular-tone regulating properties, an anti-hypoxic effect (hypoxia—lack of a sufficient supply of oxygen) and experimental inhibitory activity in cerebral edema and neurotoxicity, and also helps to modulate cerebral energy metabolism. In clinical practice the extract has a protective, curative, and modulating effect against a wide spectrum of pathological processes.

Numerous pharmacological and clinical studies of ginkgo leaf extract have demonstrated a positive effect in increasing vasodilation and peripheral blood flow rate in capillary vessels and end-arteries in various circulatory disorders, Reynaud's disease, varicose conditions, post-thrombotic syndrome (Weiss, 1988; Liberti, 1988), chronic cerebral vascular insufficiency (Vorberg, 1985), short-term memory improvement (Hindmarch, 1988), cognitive disorders secondary to depression, dementia (Warburton, 1988), tinnitus (Meyer, 1988), vertigo (Claussen, 1988), obliterative arterial disease of the lower limbs (Bauer, 1984), a protective effect against hypoxia in normal healthy males (Schaffler and Reeh, 1985), and other conditions.

The Ginkgolides

In addition to looking further into specific aspects of Ginkgo Biloba Extract (GBE) itself, future ginkgo research will undoubtedly focus on investigating the activity of individual chemical components, such as the ginkgolides. The ginkgolides, bitter diterpene principles of the leaves and roots, were first isolated in 1932 by Furukawa. The chemical structure of ginkgolides was elucidated and named by Japanese researchers Nakanishi *et al.* in 1966 (Nakanishi, 1988). They are extremely complex molecules unique to ginkgo and derive from one the most intricate natural molecular frameworks.

Using a highly complex multistep procedure, E. Corey *et al.* (1988), chemists at Harvard University, recently succeeded in completely synthesizing Ginkgolide B (Boralle, Braquet, and Gottlieb, 1988).

The various ginkgolides have different degrees of potency. Ginkgolide B is considered the most active. They are very selective antagonists of platelet aggregation induced by platelet-activating factor (PAF), an inflammatory autacoid. Autacoids, generally synthesized in local tissue sites, mediate local types of tissue response, such as pain perception, blood coagulation, and smooth muscle contraction. PAF is involved in various inflammatory, cardiovascular, and respiratory disorders. The ginkgolides modulate various enzyme systems and ion pumps, all serving to help explain their broad-spectrum therapeutic potential (Michel and Hosford, 1988). Ginkgolides counteract the effects of PAF in human and rabbit blood platelets, both *in vitro* and *ex vivo* (Braquet, 1985).

The use of PAF receptor antagonists, such as the ginkgolides, has recently raised hope that they may be used in a wide variety of human diseases. The use of ginkgo leaves for human disease, now known to be affected by PAF antagonists, has a long history. The specific extract of ginkgo leaf has been extensively studied and used for many years in West Germany and France for the treatment of cerebral and peripheral vascular disease. Only rare association of minor and reversible side effects have been observed. Further studies of the ginkgolides in other disease conditions are warranted, given the potential broad role of PAF receptor antagonists (Chung and Barnes, 1988). The ginkgolides should be considered pharmacologically and clinically distinct from GBE. Pure ginkgolides are currently available only to a handful of researchers.

Clinical Studies

Clinical studies indicate use of the well-defined standardized extract in the treatment of common conditions of elderly populations, including dizziness, depression, ringing in the ears (tinnitus), vasoconstriction, short-term memory loss, prevention and treatment of various stages of dementias, improvement in peripheral and cerebral blood flow, a protective effect on the blood-brain barrier, and an anti-radical effect (Braquet, 1988; Weiss, 1988; Liberti, 1988).

Hindmarch (1988) reported on the effects of oral administration of the standardized *Ginkgo biloba* extract (GBE) on the short term memory of healthy young volunteers (ages 25-40 years). In a double-blind cross-over trial, Hindmarch found that, one hour following a single oral 600 mg dose of GBE, short-term memory parameters were significantly improved compared with controls. According to Hindmarch, the battery of tests indicates a specific activity on central cognitive processes and he proposes the use of GBE in cases and conditions where memory problems are a feature.

Warburton (1988) reviews the results of 20 clinical studies, including two double-blind crossover studies, nine double-blind studies, eight open studies, and one open-multicenter study. The dose used in most of the studies was 120 mg extract GBE per day. A number of studies used 160 mg per day and, in some cases, doses up to 360 mg were administered. Overall, however, Warburton sees no advantage in using doses of 160 mg per day in long-term applications. Estimates of overall efficacy ranged from 44 to 92 percent. He concludes that many categories of elderly patients could benefit from GBE.

As well as supporting frequent use in patients suffering from vascular disorders, Warburton considers the data also show that GBE should be useful in dementias generally, including cerebral impairment of organic etiology, and in patients with decreased intellectual function associated with depressed states, given the positive effect of GBE on mood. Warburton also believes that these preparations should be used at the onset of symptoms associated with cerebral deficits, so that patients could lead normal lives, avoiding hospitalization.

Warburton's review indicates GBE was devoid of toxic side effects, except for minor reversible gastric disturbances. In addition to the studies reviewed, he also cites one exhaustive analysis involving 2,855 patients. This reported a higher incidence of mild gastric disturbances (still only 3.7 percent). Other very rare side effects included headache, dizziness, and vertigo, which, as Warburton states, seems paradoxical, "in view of the high level of success of EGb [GBE] in this type of symptom."

More recently, in a multicenter study involving 8,505 patients observed over 6 months, Stalleicken and Ihm (1989) reported the total incidence of adverse effects to be 0.4 percent. These were all of a minor nature and reversible. Gastric upsets were again the most common at 0.1 percent. All of these analyses and studies were done using the German extract described above. Given such data, as well as a long history of use, plus the results of all other studies of the last 15 years, safety seems well established.

A recent retrospective critical review analyzed the quality and methodology of 40 clinical trials (published since 1975) on the use of ginkgo extracts in cerebral insufficiency. The outcome of the trials (all of which reported positive results) were interpreted in relation to their quality. Clinical trials reporting results in healthy volunteers were excluded. For most of the studies the dosage was 120 mg/day of the ginkgo extract (given for at least 4-6 weeks). Of the 40 studies, eight were deemed well-performed. The authors concluded that the results of the evaluation of these ginkgo studies were consistent with the quality of scientific research on a conventional pharmaceutical drug. The authors of this review noted that they both might try ginkgo for symptoms for which the extracts are indicated, given that no clear side effects are reported. However, they stress the need for additional trials, in which double-blindness is checked, a larger number of patients are involved, with better descriptions of randomization procedures, patient characteristics, and more effective measurement of data (Kleijnen and Knipschild, 1992). For additional recent comprehensive reviews on all aspects of ginkgo see Defeudis (1991), and Huh and Staba (1992).

Summary

In summary, *Ginkgo biloba*, termed a living fossil, has survived for 200 million years. Its longevity can be attributed to its adaptability and resistance to disease which result in part from its complex and unique biochemical products. The leaves, whose use was first recorded in Chinese herbals 500 years ago, have historically been used in China to improve brain function, treat bronchitis, and other ailments. Modern science provides a rational scientific basis for traditional uses of the leaves. Given its long history of safe use as a healthful beverage tea in Asia, and the extensive clinical experience in Europe in the last two decades, this valuable plant-derived product will undoubtedly become more widely known and used in the U.S.

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PEPPERMINT

Mentha x piperita



Steven Foster



Botanical Series - 306

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On the cover:

Peppermint, *Mentha x piperita*. Photo © 1996 Steven Foster.

PEPPERMINT

Mentha x piperita

by Steven Foster

Peppermint has been a popular domestic remedy for digestive ailments for at least two centuries, and is currently one of the most economically important aromatic/medicinal crops produced in the U.S. The plant or its products are available in most parts of the world for flavoring, cosmetic, and medicinal uses. Scientific studies have confirmed a rational basis for traditional uses of the plant, while suggesting further safe and effective use of peppermint oil products as a direct or adjunct therapy in modern practice.

Botany

The genus *Mentha* of the mint family (Lamiaceae or Labiatae) includes about 20 true species, but because of hybridization, there are dozens, even hundreds of variations. In fact there are as many as 2,300 named variations, half of which are synonyms, while the rest are legitimate infraspecific names (Tucker, Harley, and Fairbrothers, 1980). While long thought to be a distinct species, peppermint (*Mentha x piperita* L.) is now believed to be a hybrid of spearmint (*Mentha spicata* L.) and water mint (*Mentha aquatica* L.) (Murray, Lincoln, and Marble, 1972). It was once believed to be a hybrid between *M. aquatica* and a cross of *M. spicata* and *M. rotundifolia* (Ruttle, 1938).

Peppermint is a perennial native to Europe, growing to three feet in height, and spreading by runners traveling across the soil surface. The stems are usually reddish-purple and smooth. The leaves are often longer and less wrinkled than those of spearmint. Flowers are pinkish or lilac.

Historically, peppermint has variously been considered as a botanically unstable species, subspecies, or variety of various mints, producing a high percentage of menthol in its essential oil, or with oils possessing the properties of peppermint oil.

Commercial Development

It is unclear whether peppermint oil was produced in the middle ages (Gildemeister and Hoffman, 1900). The herbarium of the English botanist John Ray (1628-1705) includes one of the oldest specimens of peppermint, first observed by Dr. Earles and collected in Hertfordshire County in the south of England. Ray described the plant in his *Synopsis Stirpium Britannicarum* (1696), using a lengthy Latin phrase. In Ray's *Historia Plantarum* (1704), he described the plant as "*Mentha palustris*, peper mint." By the time of publication of the third edition of Ray's *Synopsis*, he declared that the mint was superior to all mints for stomach weakness and diarrhea (Flückiger and Hanbury, 1879).

Commercial cultivation of peppermint is recorded in England as early as 1750. However, as late as 1805, it was still not grown in the famous peppermint-producing area of Mitcham. On the European continent, its commercial cultivation is recorded near

Utrecht in 1770. English production reached a peak by 1850, by which time American producers began to provide stiff competition (Flückiger and Hanbury, 1879).

Initial production in the United States is recorded in the 1790s in Cheshire, Berkshire County, Massachusetts. By 1812, peppermint was cultivated commercially for oil production in Ashfield, Massachusetts. Subsequently, production spread to New York, Ohio, and Michigan. From 1839-1889, peppermint production became a big business in these states (Landing, 1968). Today peppermint, primarily grown for essential oil production, is commercially produced in Indiana, Wisconsin, Oregon, Washington, and Idaho.

In 1995 U.S. peppermint oil production totaled \$129.3 million, up from the \$109.2 million value of the 1994 crop; production increased by 27 percent. Favorable growing conditions in most production areas resulted in a production increase to 78.3 kg per hectare (compared with an average of 77.5 kg per hectare in 1994). The price per pound was down from 1994 (\$14.60/lb.) to \$13.70/lb. in 1995. The volume of U.S. exports of peppermint oil was up over the previous year, though the total value of the crop was higher, totaling \$74.6 million (as compared with \$66.9 million in 1994). In 1995 4,290 metric tons of peppermint oil were produced in Idaho, Indiana, Oregon, Washington, and Wisconsin on 54,760 hectares (Pumphrey 1996).

Historical Use

While the medicinal and culinary use of mints has a recorded history of several millennia, a clear historical record of the use of plant material deemed *Mentha piperita* does not emerge until the beginning of the eighteenth century. By 1721 it became an official item of materia medica in the London Pharmacopoeia as *Mentha piperitis sapore* (Flückiger and Hanbury, 1879).

In American herbal traditions, peppermint (as "*Mentha peperita*" L.) is first described in Samuel Stearn's *The American Herbal* (1801). "It is raised in some of our gardens," Stearn writes. "It is a stimulant. It restores the functions of the stomach, promotes digestion, stops vomiting, cures the hiccups, flatulent colic, hysterical depressions, and other like complaints. It does not heat the constitution so much as might be expected."

"Dose, Of the juice from an ounce to one and an half. The leaves when dry may be drank as a tea. Of the oil from one to two drops in sugar. Of the distilled water, from one to two ounces."

Peppermint leaf, dried and fresh, and the essential oil distilled from fresh or dried leaves, are widely used in foods, pharmaceuticals, cosmetics, and folk medicine. Peppermint leaf tea is used for indigestion, nausea, diarrhea, colds, headache, and cramps. It is valued for aromatic, stomachic, stimulant, and antispasmodic properties (Leung & Foster, 1996). The major use of the oil is for flavoring toothpastes and other mouth care products, as well as chewing gums. The high price of peppermint oil thwarts its use as a material for the production of menthol (Bauer and Garbe, 1985).

Peppermint oil has been shown to have antimicrobial activity. Peppermint extracts have shown antiviral activity against Newcastle disease (a contagious of fowls transferable to humans causing a severe conjunctivitis), herpes simplex, and other viruses. Oil of peppermint is experimentally antispasmodic (Leung & Foster, 1996).

Menthol is the primary component of the essential oil of peppermint (29 to 48 percent). Other constituents include menthone (up to 31 percent), methyl acetate (up to 10 percent), menthofuran (up to 7 percent), and limonene. Peppermint herb also contains flavonoids, phytol, tocopherols, carotenoids, betain, choline, azulenes, rosmarinic acid, and tannins (Leung & Foster, 1996). While menthol is a major component of peppermint oil, Der Marderosian and Liberti (1988), Weiss (1988), and Leung and Foster (1996) warn of toxic effects of ingestion or external application of purified synthetic menthol (artificially produced by the hydrogenation of thymol). Menthol is also extracted from the volatile oil of Japanese mint (*Mentha arvensis*) which is considerably higher in menthol content than peppermint, but considered inferior for flavoring purposes. Menthol should be considered a distinct product from the volatile oil of peppermint.

Peppermint enjoyed clinical use among physicians in the late nineteenth and early twentieth centuries. Ellingwood (1902) recommends peppermint water (distillate) for "flatulent colic, gastrodynia, nausea, vomiting, spasmodic pain in the bowels, hiccough, palpitation from indigestion, griping, cholera morbus, cholera infantum, spasmodic cholera, irritability of the stomach, diarrhea with abdominal pain, nervous headache, [and] painful gonorrhea."

Modern Use

In recent years the medical community has begun to shift its focus from merely recognizing peppermint oil as a pharmaceutical flavoring material to investigation and confirmation of its therapeutic value. Rees, Evans, and Rhodes (1979) reported results of a clinical trial with 18 patients with active irritable bowel syndrome. This condition, though not fully understood, is characterized by recurrent colicky abdominal pain, a feeling of distention, and variations in bowel habits. According to Murray (1987), irritable bowel syndrome represents between 30 to 50 percent of all referrals to gastroenterologists and is the most common gastrointestinal ailment seen by physicians. As much as 15 percent of the population may be affected by this condition. In the trial by Rees *et al.*, patients received either enteric-coated peppermint oil capsules (to prevent absorption in the stomach) or peanut oil capsules as placebo. One to two capsules were administered three times per day, depending upon the severity of symptoms. Treatment periods lasted three weeks.

The authors noted that patients felt considerably better and experienced relief of abdominal symptoms while taking peppermint oil capsules compared with the placebo. The relative lack of side effects coupled with a reduction of symptoms of irritable bowel syndrome suggested to the authors that the use of enteric-coated peppermint oil capsules is a useful treatment for symptoms associated with this condition. Occasionally peppermint oil is released into the stomach causing heartburn and relaxation of the lower esophageal sphincter. The treatment is contraindicated with meals and patients with achlorhydria, absence of hydrochloric acid from gastric juices (Rees, Evans and Rhodes 1979). Dosage of enteric-coated peppermint capsules is recommended between meals. ,

Somerville, Richmond, and Bell (1984) studied the pharmacokinetics of enteric-coated peppermint oil capsules by determining menthol metabolites in urine. These researchers found that enteric-coated peppermint oil capsules significantly delayed the appearance of menthol metabolites in urine, suggesting that the oil in the enteric-coated

peppermint capsules is released in the colon. The oil in gelatin-coated peppermint capsules, on the other hand, is absorbed in the stomach. The authors note that for peppermint oil to be effective in the treatment of spastic colon syndrome, the oil must reach the colon in an unmetabolized state (Somerville, Richmond, and Bell, 1984).

A communication by Leicester and Hunt (1982) to the British medical journal *The Lancet* indicated that peppermint oil may be useful as an adjunct to colonoscopy. Recognizing that peppermint oil is a safe substance and produces local smooth muscle relaxation, these researchers used peppermint oil in colonoscopy to reduce colonic spasm during the diagnostic procedure. Colonic spasm was relieved within 30 seconds in each of 20 patients using this technique. The workers switched from peppermint oil B. P. (*British Pharmacopoeia*) to a diluted suspension of peppermint oil in order to avoid any direct irritation from the oil. Antispasmodic drugs usually used in the procedure have to be administered intravenously while the patient is in an inconvenient, uncomfortable position. However, diluted peppermint oil, sprayed onto the endoscope itself, was thought to be a more convenient means of producing colonic relaxation during endoscopy than orthodox pharmaceuticals generally used in the procedure (Leicester and Hunt, 1982).

Other studies have shown that peppermint oil inhibits gastrointestinal smooth muscle spasms (Sigmund and McNally, 1969; Taylor, Luscombe and Duthie, 1983) and reduces colonic motility (Duthie, 1981) in humans. Inhalation of the oil for treating congestion due to common colds is believed to ease congestion, aiding respiration, by stimulating cold receptors in the respiratory tract (ESCOP, 1992). Numerous studies provide further information on the efficacy and mechanism of peppermint or peppermint oil in laboratory experimental models.

According to a recent proposed European monograph (ESCOP, 1992) internal use of the oil, only under the direction of a physician, is indicated for spastic conditions of the upper gastrointestinal tract, flatulence, symptomatic treatment of irritable bowel syndrome, and catarrh of the respiratory tract. It is contraindicated for gall bladder inflammation and gall stones. External use includes oral mucosa inflammations, rheumatic conditions, local muscle and nerve pains as well as skin conditions such as pruritus and urticaria. Peppermint leaf is approved by the Commission E of the German government as a nonprescription medicine for dyspeptic complaints and peppermint oil is approved for treatment of irritable bowel syndrome. However, Commission E contraindicates peppermint oil topically on the face of children under four years old as well as internally for gallstones. (Blumenthal, *et al.*, 1996).

Peppermint and peppermint oil are some of the most widely-used flavors in the food and confection business. Additionally, scientific research confirms traditional folk remedy use of peppermint as a digestive aid.

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CHAMOMILE

Matricaria recutita
& *Chamaemelum nobile*



Steven Foster

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On the cover:

Chamomile, *Matricaria recutita*. Photo ©1996 Steven Foster

CHAMOMILE

Matricaria recutita

&

Chamaemelum nobile

by Steven Foster

The chamomiles (or camomiles) have long been used and cultivated by Europeans and Americans. There is hardly one western herbal published in the past 500 years that does not include this group of plants. Tyler (1993) notes that the Germans refer to it as alles zutraut (capable of anything), equating its reputation (though not uses) as a popular European herb with the status afforded ginseng in other cultures.

Nomenclature

The word chamomile is derived from the Greek *chamos* (ground) and *melos* (apple), referring to the plant's low growing habit and the fact that the fresh blooms are somewhat apple-scented (Smith, 1963).

According to Hill (1948), accurate identity of a plant under discussion as "chamomile" is hampered by the fact that the name has been applied to a dozen or more species in six genera of the aster family (Asteraceae or Compositae). However, of all these plants, only two species are generally utilized in the herb trade and in broad historical folk usage.

Unfortunately for the botanist and lay person alike, both of those species have, in the past 20 years, been referred to by as many as five different Latin species names, as well as a number of common names. Tucker (1986; Tucker *et al.*, 1987, 1989) retains *Chamomilla recutita* (L.) Rauschert as the proper botanical name of the "common chamomile" of the European continent, better known as Hungarian or German chamomile, also known by the synonyms *Matricaria chamomilla* and *M. recutita*. Tucker and co-workers cite Kay *et al.* (1976) as the authority. However, Jeffery (1979) provides convincing evidence for relegating the genus name *Chamomilla* to synonymy with *Matricaria*. Conveniently, *Matricaria recutita* is the name cited in *Hortus Third* (Liberty Hyde Bailey Hortorium, - 1976). This book has been widely used as a source of botanical names by the American herb trade. The unfortunate part of this taxonomic shuffling is that the lay person, herb trader, or research scientist must source information on the plant under at least three different Latin names, depending upon the year of publication. Such a complex problem for a simple herb! Henceforth, we will deem the major source plant of the chamomile of commerce *Matricaria recutita*, "German chamomile," at least until a taxonomist provides a more definitive interpretation of the nomenclature.

Let's turn to the "common chamomile" of England, better known as English or Roman chamomile. In many herb books published prior to 1976, this plant is called *Anthemis nobilis* L. However, in 1785, an Italian botanist, Carlo Allioni (1728-1804), placed this plant in the genus *Chamaemelum*, naming it *Chamaemelum nobile* (L.) All.

Buried in obscurity for nearly 200 years, the name resurfaced in the mid-1970s and was adopted in volume 4 of *Flora Europaea*, as well as *Hortus Third*. It is again retained by Tucker (1986; Tucker *et al.*, 1987, 1989). *Chamaemelum nobile* is best known as Roman chamomile, the name by which we will refer to it here. The name Roman chamomile was first bestowed upon the plant by Joachim Camerarius in 1598, after observing it growing abundantly in the vicinity of Rome (Flückiger and Hanbury, 1879).

History

German chamomile is a sweet-scented, smooth, branched annual growing to 2 1/2 ft. in height. It is native to Europe and Western Asia, and has become widely naturalized in the U.S. (L. H. Bailey Hortorium, 1976).

Roman chamomile is an aromatic, creeping perennial, growing to one foot in height. It hails from the United Kingdom (UK) and is widely grown in American herb gardens.

Historically, Roman and German chamomiles have been used interchangeably or confused. The German is preferred on the European continent, while the Roman chamomile has been more widely used in the U.K. In the U.S., German chamomile is by far the most widely consumed of the two species. Despite the fact that the two plants have often been lumped together as “chamomiles,” their chemical components and essential oils are quite different, and each should be treated as a separate entity (Mann and Staba, 1986). In addition to genetic differences, quality and quantity of essential oil and other plant components, as in most medicinal plants, are dependent upon a wide range of variables such as environmental factors, cultivation practices, plant part, plant age, and postharvest handling. Articles relative to these subjects are cited by Mann and Staba, (1986) and Simon, Chadwick, and Craker (1984).

German chamomile has a long tradition as a folk or domestic remedy used for a wide variety of purposes including an external compress or fomentation for sciatica, gout, lumbago, inflammations, rheumatism, and skin ailments. A tea (infusion), decoction, or tincture has long been used for treating colic, convulsions, croup, diarrhea, fever, indigestion, insomnia, infantile convulsions, toothache, bleeding or swollen gums, a folk cancer remedy, and many other uses. Historically, Roman chamomile has been utilized for similar purposes. It is best known as a pleasant-tasting, or healthful beverage tea (Leung & Foster, 1996; Duke, 1985).

Safety

In the late 1970s and the 1980s several popular and scientific articles strongly warned against drinking chamomile tea, the warning based on an isolated report of anaphylactic reaction resulting from drinking chamomile tea (Casterline, 1980; Benner and Lee, 1973). One report (Hausen, 1979) tested 25 human subjects known or thought to be allergic to aster family members, and found that two of the patients (8 percent) were allergic to chamomile. Cross-reactions with other aster family members were also observed.

Mann and Staba (1986) suggest that a possible source of allergic reactions attributed

to chamomile flowers may be other closely related, more allergenic plants, such as *Anthemis cotula*, dog fennel or mayweed, which is known to cause toxic or irritating reactions, and is sometimes offered as or may be an adulterant to chamomile. These authors suggest proper identification and purity of chamomiles as a preventative measure, but warn that those with known sensitivities to aster family members (including ragweed, asters, chrysanthemums, etc.) may best be advised to avoid German and Roman chamomiles and their products.

In the proposed European monograph on chamomile flowers produced by ESCOP (European Scientific Cooperative for Phytotherapy) there are several headings that address issues relative to potential side effects or adverse reactions. These include headings for contraindications, side effects, use during pregnancy and lactation, special warnings, interactions, duration of administration, and overdose. Under contraindications, we find "none known." Use during pregnancy and lactation? "No adverse effects reported." Special warnings? "None required." Interactions? "None reported." Duration of administration? "No restriction." Overdose? "No intoxication symptoms reported." The side effect heading in the ESCOP monograph reads, "Extremely rare contact allergy" (ESCOP, 1990). What is rare? Tyler (1993), while reiterating a word of caution for those who suffer from hypersensitivity to ragweeds and other aster family members, notes that normal persons should not be deterred from consuming the herb. He cites a survey of world literature (Hausen, Busker, and Carle, 1984) which found only about 50 reports of chamomile allergies reported between 1887 and 1982. Only five of these reports were attributed to the widely available German chamomile (*Matricaria recutita*). The vast majority involved the genus *Anthemis*, primarily *Anthemis cotula*, which is not in commerce. These reports, however, emphasized the need for proper identification of source plants used in herbal preparations. The Commission E, an expert panel of the German Institute for Drugs and Medical Devices, concurs that there is no known adverse reactions nor contraindications for the nonprescription drug use of German chamomile (Blumenthal, *et al.*, 1996).

Contemporary Medicinal Use

Azulenenes, a group of chemical components found in both species of chamomile, possess experimental antiallergenic activity (Farnsworth and Morgan, 1972; Mann and Staba, 1986). Both histamine release and inhibition of histamine discharge have been advanced as mechanisms for the potential antiallergenic action of azulenes. Mann and Staba (1986) suggest that, since azulenes seem to prevent allergenic seizure, inhibition of histamine is probably involved in the true mechanism of their action.

In modern Europe, chamomile products, including extracts, tinctures, tisanes (teas), and salves, are widely used as anti-inflammatory, antibacterial, antispasmodic, and sedative agents. Extracts are used to allay pain and irritation, clean wounds and ulcers, and aid prevention and therapy of irradiated skin injuries, as well as treat cystitis and dental afflictions (Mann and Staba, 1986). The plant is included in the pharmacopeias of 26 countries (Salamon, 1992).

The German Commission E approves German chamomile preparations for external use in cases of inflammations of skin and mucous membranes, bacterial skin diseases,

diseases of mouth and gums, inflammation and irritation of the upper respiratory tract, and inflammations of the ano-genital area by using chamomile baths. Internally, chamomile is approved for gastrointestinal spasms and inflammatory diseases of the gastrointestinal tract. The flowers must have a minimum of four percent essential oil (Blumenthal, *et al.*, 1996).

Extracts and a number of components of chamomile, including azulenes (chamazulene) and alpha-bisabolol, have been shown to have anti-inflammatory activity. Chamazulene, comprising 5 percent of the essential oil, is an artifactual component formed during heating of teas and extracts (Der Marderosian and Liberti, 1988). This activity has been demonstrated, not only by long empirical use, but by a number of different laboratory models as well. Studies also show that alpha-bisabolol has a protective effect against peptic ulcers, as well as antibacterial and antifungal activity. Alpha-bisabolol has also been shown to reduce fever and shorten the healing time of skin burns in laboratory animals (Der Marderosian and Liberti, 1988). These two compounds are considered primary active components in German chamomile. Many commercial German chamomile preparations are standardized to chamazulene and alpha-bisabolol content (Tyler, 1993; Mann and Staba, 1986).

Four basic chemical types of *Matricaria recutita* (A, B, C, and D) are now recognized according to qualitative and quantitative analysis of the essential oil. Consequently, in the major chamomile production countries (Argentina, Czech Republic, Germany, Hungary, Poland, and Slovakia), intensive plant improvement programs have been initiated to produce plants with high levels of defined chemical components (Salamon, 1992).

About 120 secondary metabolite chemical constituents have been identified in chamomile, including 28 terpenoids, 36 flavonoids, and 52 additional compounds, all with potential pharmacological activity (Salamon, 1992). Components in the essential oil of German chamomile contribute to its smooth muscle relaxing activity. Nonvolatile constituents, including flavones (apigenin, luteolin, patuletin, and quercetin) are also antispasmodic (Tyler, 1993). Chamomile teas absorb only about 10-15 percent of the essential oil available in the flowers, but, if used over a long period of time, have the potential for a cumulative therapeutic effect (Der Marderosian and Liberti, 1988; Farnsworth and Morgan, 1972).

Summary

Chamomiles have been used for centuries in teas as a mild, relaxing sleep aid, treatment for fevers, colds, stomach ailments, and as an anti-inflammatory, to name only a few therapeutic uses. Extensive scientific research over the past 20 years has confirmed many of the traditional uses for the plant and established pharmacological mechanisms for the plant's therapeutic activity, including antipeptic, antispasmodic, antipyretic, antibacterial, antifungal, and antiallergenic activity. In addition to medicinal use, chamomiles enjoy wide usage, especially in Europe, Latin America, and the U.S., as a refreshing beverage tea and as an ingredient in numerous cosmetic and external preparations. One source estimates that over one million cups of chamomile tea are ingested worldwide each day (McCaleb, 1990).

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AMERICAN GINSENG

Panax quinquefolius



Steven Foster

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On the cover:

American ginseng, *Panax quinquefolius*. Photo ©1996 Steven Foster.

AMERICAN GINSENG

Panax quinquefolius

by Steven Foster

American Ginseng, Panax quinquefolius L., has been one of the best-known American medicinal plants since its discovery over 280 years ago. Since the eighteenth century, the vast majority of both wild-harvested and cultivated supplies of American ginseng have been exported to the Orient. The subtle biological activity of ginseng, along with conflicting results and interpretation of studies, has produced an enigma in assessing the plant's value in health. While more questions than answers about predictable benefits of American ginseng exist, investigations conducted over the past 15 years have sharpened scientific focus in directing research efforts for the future.

Discovery

A 1714 publication of Father Petrus Jartoux (1668-1720), a Jesuit missionary in North China, provided the first published Western account of the Asian *Panax ginseng*. After describing the plant's habitat, Jartoux made a remarkable conjecture. "All of which makes me believe," he writes, "that if it is to be found in any other country in the world, it may be particularly in Canada, where the forest and mountains, according to the relation of those that have lived there, very much resemble these here" (Jartoux, 1714).

In 1715 Jartoux's words reached Joseph Francois Lafitau (1681-1746), a Jesuit missionary working among the Mohawks above Montreal. After three futile months of searching, he stumbled upon American ginseng quite by accident in 1716. His discovery was detailed in an 8,000-word letter to his superior, the Duke of Orleans, Regent of France, in 1718. He apparently sent specimens to Michel S. Sarrazin (1659-1734) who, in the same year, described American ginseng and its discovery in Canada (Foster, 1986; Foster, 1989; Duke, 1989).

Lafitau sent samples of dried roots to Jartoux. Jartoux showed them to Chinese merchants, and was able to arrange importation of the roots to China, provided they were cured as prescribed by the Chinese. Thus began the export of American ginseng to the Orient (Goldstein, 1975).

Nomenclature

The genus *Panax* of the ginseng family (Araliaceae) contains about six species, four native to eastern Asia, and two indigenous to eastern North America. In his *Species Plantarum* (1753, #1058) Linnaeus named American ginseng *Panax quinquefolium*. The name has remained relatively stable, but debate has existed as to whether the specific epithet should end with the masculine "us" (*P. quinquefolius*) or the neuter "um" (*P. quinquefolium*). While some argue for the neuter ending as it appeared in the work of Linnaeus, according to Graham (1966) and Tucker *et al.* (1989), the International Code of Botanical Nomenclature (article 76) dictates that this specific epithet must be treated

as a masculine, thus should be *Panax quinquefolius*. *Panax* derives from Greek roots, *pan* meaning “all,” and *akos*, “cure,” referring to the “cure all” or “panacea” attributes of the root’s healthful virtues. “Ginseng” means “essence of the earth in the form of a man” (Graham, 1966).

Distribution and Trade

Panax quinquefolius occurs on rich, rocky, shaded, cool slopes, preferring sweet soils. It is found in eastern North America, from Quebec to Manitoba, south to northern Florida, Alabama, and Oklahoma. Its peak abundance is in the Cumberland Gap region of the southern Appalachian. Elsewhere it is rare (Eastman, 1976). Once considered frequent in eastern North America, it is now considered a threatened, rare, or endangered species in many areas due to overzealous harvest of the root for commercial purposes (Lewis and Zenger, 1982). The international trade of American ginseng is regulated under the provisions of CITES (Convention on International Trade in Endangered Species), which regulates trade through permit requirements for imports, exports, and re-exports of listed species. American ginseng is listed in CITES Appendix II, controlling and monitoring its trade “in order to avoid utilization incompatible with [its] survival” (Singer, 1979). Harvest and commerce are regulated and restricted both jointly and separately by state agencies, the U.S. Fish and Wildlife Service, and the United States Department of Agriculture.

Soon after American ginseng was discovered by Lafitau, exports of the root from Canada reached China. Early shipments from the U.S. went to the China by way of France or England. In 1773 a sloop, the “Hingham,” carried 55 tons of ginseng from Boston. A direct shipment to China after the American Revolution was made in 1782 by a New York merchant, John Jacob Astor (Williams, 1957). For the four years in which records of ginseng exports were kept in the 1770s, an average of 140,000 pounds was exported each year. Near the turn of the eighteen and nineteenth centuries, ginseng exports seem to virtually disappear (at least from government records).

Pursh (1814, p. 191) observed the decline in interest in the plant, “it formerly was an article of exportation in America, but at present there is little demand for it.” Jacob E. Bigelow (1824, p. 376) makes a similar observation, “The root of Ginseng is in high estimation among the Chinese and formerly constituted a profitable article of export to Canton.”

Export of wild-harvested root picked up again in the mid-nineteenth century. Exports of 1858 are documented at 366,053 pounds (Krochmal and Krochmal, 1977). Cultivation of American ginseng was begun in the 1870’s by Abraham Whisman of Boones Path, Virginia. By 1895 there were about twenty ginseng growers. A USDA Bulletin on American ginseng cultivation, published in 1895 resulted in a boon of start-up ginseng growers (Williams, 1957). In 1995 1,552,324 pounds (704,130 kg.) of cultivated ginseng root, valued at \$44,905,434, was exported from the U.S., while 358,260 pounds (162,506 kg.) of wild-harvested root, valued at \$31,457,267, was exported. (D. A. Pumphrey, 1996).

History of Use

Relatively little is known about the use of American ginseng by native groups.

Ginseng was one of the five most important medicines among the Seneca Indians, primarily used by the elderly. A Crow legend holds that Gray Bull's wife had revealed to her in a dream that chewing the root would induce childbirth without suffering. An infusion of the boiling leaves was equally effective when drunk by the woman (Goldstein, 1975). The Oklahoma Seminole used the root to cure nosebleed, treat shortness of breath, and as a "woman catcher" (Howard, 1984).

The Penobscots steeped the root in water, drinking the infusion from time to time to increase the fertility of women. The Penobscot referred to the plant as "man root" (Speck, 1915). While not observed to use the root, it was harvested for sale by the Ojibwe, who followed the ethical practice of harvesting the roots only when the red berries were mature, and before they were ready to drop. The whole fruiting tops were planted in the hole from which the roots were dug, thus helping to insure long term sustainable harvest (Smith, 1932). The Menominee used the root as a tonic and to strengthen mental powers (Smith, 1923). Further ethnobotanical uses are noted by Vogel (1970) and Moerman (1986).

Early Western medical observations on the use of American ginseng attempted to find active qualities which would justify the high esteem for the plant held by the Chinese. The results were conflicting, setting the stage for an on-going argument on the health value of American ginseng.

Porcher (1849) quoting numerous botanical and medical writers, attempts a balanced assessment. "...it is a restorative after great fatigue, as an antispasmodic in nervous affections, in coma, and as an aphrodisiac...Dr. Wood, [*U.S. Dispensatory*, 1847] says, it is very little more than a demulcent (soothing for mucous tissue); but Lindley [*A Natural System of Botany*, 1836] thinks that there is not reasonable doubt of the ginseng having an invigorating and stimulant power, when fresh."

Primarily consumed by Asians, American ginseng has always been regarded as an export commodity. It never became a major medicinal plant in the American materia medica, of either allopathic or Eclectic medicine. The root was official in the *United States Pharmacopeia* from 1842 to 1882. It was primarily used as a stimulant and a stomachic (Claus, 1961).

According to Hsu (1979) there are five basic reasons explaining why the Chinese favor American ginseng. First, when American ginseng was initially exported to China in the early eighteenth century, wild *Panax ginseng* (Asian ginseng) had already become extremely scarce. The relative abundance and quality of wild American ginseng, opened the way for development of cultivated American ginseng as an export crop in the early twentieth century. Psychologically, Asians have believed U.S. manufactured or produced products to be of superior quality. The taste of the American ginseng is sweeter than Asian ginseng. Last, American ginseng (*P. quinquefolius*) and Asian ginseng (*P. ginseng*) are considered to be distinct medicinal plants. American ginseng is considered more *yin* in Chinese traditions, and is good to reduce heat of the respiratory or digestive systems. Conversely, *P. ginseng* is more *yang*, and is a heat-raising tonic for the blood or circulatory system. Consequently, American ginseng is preferred by consumers in subtropical and tropical regions of Asia, as it is a cold or mild tonic, that will reduce "heat" in the system, while acting as a general tonic.

The large majority of the 2,900 documented citations to ginseng refer to studies on

the Asian *Panax ginseng*. A much smaller number of scientific studies have involved American ginseng. The focus of Oriental researchers is aimed at *how* ginseng works, since it is culturally accepted that it does work. On the other hand, Western researchers focus efforts on determining *if* it indeed works at all (Braly, 1987).

Modern Use

Inconsistencies in interpreting results of various ginseng studies are documented by Lewis (1986). Conflicting opinions have often been the result. Further complicating the interpretation of the efficacy or usefulness of ginseng are the variations or differences in plant and animal species studied, plant parts used, differences in extractions and purification methods, and differences in route and dose administered. Furthermore, depending upon concentration of specific chemical components with opposite pharmacological activity, differing results may be obtained (Staba and Chen, 1979).

Saponins are considered the primary biologically active components of *Panax* species. The major saponins in *Panax* are termed ginsenosides. Ginsenosides isolated from American ginseng include Rb₁, Rb₂, Rb₃ (0.03%), Rc, Rd, Re, Rg₁ (0.15 percent), Rg₂ (0.008 percent), Ro, and F₂ (Thompson, 1987). Concentrations of total ginsenosides were reported to be higher in wild American ginseng root than cultivated root. The presence and absence of various ginsenosides has been reported (Liu and Staba 1980).

Timing of harvest is one of the variables involved in ginsenoside content. Citing the research of Soldati and Tanaka (1984), Duke (1989) notes that the highest yields of ginsenosides were obtained at the end of the summer of the fifth year. The root also doubles in weight at this time. Growth and ginsenoside increases were less marked after the fifth year.

Review of the pharmacological actions of pure ginseng saponins by S. Shibata *et al.* (1985) indicates that ginsenoside Rg₁ has shown weak CNS (central nervous system)-stimulant activity, anti-fatigue action, and aggravation of stress ulcer, and a slight increase in motor activity. In behavioral tests it showed an acceleration of discrimination behavior in pole-climbing tests and Y-maze tests, a reversal learning response in the Y-maze test, and one-trial passive avoidance learning using the step down method. Ginsenoside Rb₁ has CNS-depressant activity, is anticonvulsant, analgesic, antipyretic, antipsychotic, ulcer-protective, inhibits conditioned avoidance response, has weak anti-inflammatory activity, an antihemolytic action, and increases gastrointestinal motility. In addition it accelerates glycolysis, and accelerates serum and liver cholesterol, nuclear RNA, and serum protein synthesis.

Pharmacological and clinical studies conducted over the past 40 years, primarily with *Panax ginseng*, have focused on radioprotective, antitumor, antiviral, and metabolic effects; antioxidant activities; nervous system and reproductive performance; effects on cholesterol and lipid metabolism, and endocrinological activity (Ng and Yeung, 1986; S. Shibata *et al.*, 1985). Additional studies and important review articles on the pharmacology and clinical applications of ginseng species are found in the American Botanical Council's Botanical Series monograph #303 (Asian ginseng).

Staba and Chen (1979) reviewed major pharmacological activity associated with ginseng (species not specified). Small doses of the ginsenoside Rg₁ tend toward a CNS-stimulating effect. Large doses of the same compound depress the CNS. Adaptogenic and

performance enhancing effects reported have included adaptation to dark, high and low temperatures, and work efficiency. Anti-fatigue activity has been demonstrated by swimming capacity of mice. Peripheral and neurogenic stimulation of the adrenal cortex by ginseng is suggested as a possible mechanism for coping with stress. Used externally, skin regeneration and anti-wrinkling effects have been reported. Ginseng has been shown to counteract the toxic effects of chloroform, amphetamines, and other toxins. Studies suggest it prolongs the life span of mice exposed to X-rays. Ginseng has been reported to increase the weight of seminal vesicles and prostate glands, and increase sperm counts and pregnancies. Various studies have shown that ginseng may both increase and decrease body temperature. Small doses have exhibited a tendency to increase body weight, large doses have a tendency to decrease body weight. In rat experiments, stimulation of DNA, RNA, and protein synthesis has been reported. See Staba and Chen (1979) for additional details.

Future Directions

It is only in the past 20 years that American researchers have begun to study the chemistry, pharmacology, and general biology of American ginseng. Studies on chemical components and pharmacokinetics have been conducted by researchers at the Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Minnesota under the direction of Professor E. John Staba, and by Professor Ara Der Marderosian of the Philadelphia College of Pharmacy. Studies on population dynamics, pollination, breeding systems, and demographics have been conducted by Professor Walter Lewis, Washington University.

Research on American ginseng is still in its infancy. As Professor Staba noted in a letter to the editor in *Lancet* (1985), "Evaluation of existing studies is not going to establish ginseng as a useful therapeutic agent. What we need now are long-term, controlled human studies of ginseng to identify predictable beneficial or harmful physiological effects. If such effects were to be found we might be better able to find out how ginseng works."

While questions remain regarding how and if American ginseng works, one thing is clear: the mystique and search for the truth will continue to engross scientists and non-scientists alike.

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VALERIAN

Valeriana officinalis



Steven Foster

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Botanical Series - 312

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On the cover:

Valerian, *Valeriana officinalis*. Photo ©1996 Steven Foster.

VALERIAN

Valeriana officinalis

by Steven Foster

Valerian (Valeriana officinalis L.) is a mild sedative and sleep aid that has been popularly used in Europe for several hundred years. Interest in the use of the plant has dramatically increased over the past 20 years, resulting in over 200 scientific papers on its chemistry, pharmacology and clinical applications. Given its long-standing popularity and history of safe use, current interest in the use of valerian preparations continues to grow.

Botany and Nomenclature

Valerian (*Valeriana officinalis* L.) is a highly variable member of the Valerian family (Valerianaceae) occurring in eastern, southeastern and east-central Europe, extending to south Sweden and the southern Alps. It is locally naturalized westward in Europe (Ockendon, 1976). Valerian was brought to North America by colonists at an early date. It escaped from cultivation, becoming naturalized from Nova Scotia to Pennsylvania; Ohio to Minnesota and Quebec (Fernald, 1950). The genus *Valeriana* includes upwards of 250 species of the northern temperate zone, South Africa and the Andes. Twenty species are indigenous to Europe (Mabberly, 1987). In North America (exclusive of Mexico) there are sixteen native or naturalized species, with five subspecies and two varieties.

Linnaeus noted that the plant is named in honor of *Publius Aurelius Licinus Valerianus*, Roman emperor from 253-260. The name "valerian" is also attributed to the Latin "*valere*" meaning "to be in health." (Fernald, 1950).

History

The first century Greek physician Dioscorides and his contemporaries wrote about Valerian as *Phu*, a name, which incidentally has the same word-root as our colloquial one-word exclamation "pew." The plant was rightly named in that context, as there are few roots with such a distinctive odor—at once perfume-aromatic, or to the olfactory organs of most, offensive in odor. Not to cats, though, for as with catnip and perhaps even more so, felines are attracted to the aromatic root. Cats are reported to have attempted to gain access to the herb by scratching through the labels of apothecary jars. The eighteenth century English physician, William Cullen, suggested that the quality of the valerian of apothecary's shops could be determined by how cats react to it (Cullen, 1808).

Initial publication of the word valerian comes in recipes of the Anglo-Saxon leech books of the eleventh century. The word *Valeriana* is believed to have first been used

sometime in the ninth or tenth centuries. The 1633 Thomas Johnson edition of Gerarde's *Herball* gives the old English name as *Setwall* which he notes is more properly applied to the herb Zedoary (Flückiger and Hanbury, 1879).

Valerian has been used as a flavoring as well as a medicinal herb. Among poor people of Northern England, Gerarde finds it “in such veneration amongst them, that no broths, pottage, or phsyciall meats are worth any thing, if Setwall were not at an end....”

Valerian was not a major medicinal plant of the ancient classical authors, being best known as a diuretic and emmenagogue. The second century Greek physician Galen affirmed he had used it in the treatment of epilepsy of children and adults. The Italian nobleman Fabio Colonna, born in 1567, suffering from birth with epilepsy without relief from his physicians, is said to have searched the classics for a cure. Finding mention of the use of valerian for epilepsy, he took the powdered root in half-spoonful doses, and was eventually completely restored to health. Colonna (also known as Fabius Columna) became an important sixteenth century botanical author. It was his vaunting of the virtues of valerian in the treatment of his own long-standing case of epilepsy that initially generated interest in the plant over the next five centuries (Duncan, 1789; Thornton, 1814; Eberle, 1834; Stille, 1874).

By the late 1700s many writers began to question efficacy of valerian in epilepsy. Cullen (1808) comments that it had been held in esteem for epilepsy since the time of Fabius Columna and “it has been since much taken notice of and employed in practice, frequently with success, but frequently also, particularly in my own practice, without any effect at all. The later circumstance, however, I impute to this, that the best remedies may often fail in a disease which depends upon a diversity of causes; and partly to this, that the valerian is frequently employed in an improper condition” (Cullen, 1808 Vol. 2, p. 213).

The value of valerian as an antispasmodic and sleep aid evolved out of seventeenth and eighteenth century usage. “Its antispasmodic powers in general are very well established: and I trust to many of the reports that have been given of its efficacy,” wrote Cullen. Duncan found it to be “useful in procuring sleep, particularly in fever, even when opium fails. But it is principally useful in affections of the hysterical kind” (Duncan, 1789, p. 300). It should be noted that “hysterical fits” of this time period are not to be interpreted by modern definitions of hysteria. Rather, it refers to “fits of the mother” or “womb-sickness”—conditions related to dysfunction of the *ystera* or uterus (Cole, 1655).

By the late nineteenth century, uses of valerian preparations had evolved to their modern applications “to quiet nervous excitement, as in hysteria or nervous headache, or to promote sleep in cases of hypochondriasis or nervous restlessness” (Edes, 1882).

Valerian was an official remedy in the *United States Pharmacopoeia* from 1820-1936, and official in the *National Formulary* from 1888-1946.

Modern Use

Valerian is widely used in Europe as a mild nerve sedative and sleep aid for insomnia, excitability, and exhaustion. It has depressant activities on the central nervous system, is antispasmodic, and has been described as having equalizing effects—acting as a sedative in agitated states and a stimulant in fatigue (Leung and Foster, 1996; Tyler, 1993; Williamson and Evans, 1988). Long-standing clinical experience has provided ample evidence of the value of valerian as a sedative. Discrepancies in results are due to variations in dosage, as well as quality of commercial preparations (Tyler, 1993; Weiss, 1988).

Tincture of valerian presents clinical results only if given in sufficient dosages. Efficacy is not achieved with dosages of 10-20 drops of the tincture. According to Weiss, a whole teaspoonful of tincture is needed to produce satisfactory sedative, spasmolytic (relieving smooth muscle spasms), and sleep-inducing effects. If necessary, it should be given several times daily, or repeated a number of times at 15-30 minute intervals, to achieve expected results in states of acute restlessness. He also notes, that over-dosage is highly unlikely, even in large doses (Weiss, 1988).

The sedative action of valerian has been attributed to a number of chemical fractions or components. A group of unstable compounds known as valepotriates, and some of their degradation products, have been shown to possess sedative activity. Other constituents with sedative activity include components of the essential oil such as valerenic acid and valerenone. Hazelhoff *et al.* 1979 suggest that there is an interaction between these constituents. Valerian, valerenic acid and the esters of eugenyl and isoeugenyl are spasmolytic (Hendriks *et al.*, 1981).

However, a study by Krieglstein and Grusla (1988) suggests that while valerian definitely contains central nervous system (CNS) depressant compounds, they do not correspond to those that have previously been discussed as the active components. The researchers report that valepotriates, valerenic acid, valeranone and the volatile oil of valerian were ineffective as CNS depressant agents when tested individually. An as yet uncharacterized chemical fraction was proposed as the active substance. Isolation or determination of the proposed active chemical fraction was not presented in the article.

A spasmolytic or relaxing effect on the smooth muscle system has been established for the valepotriates and other components of valerian. Therefore, Krieglstein and Grusla evaluated the pharmacological influence of valerian components on the effect on cerebral blood supply as well as cerebral glucose turnover, as parameters for determining the effect of the components on the central nervous system. Fourteen different chemical fractions and pure compounds were evaluated. An increase or decrease of neuron activity in the brain corresponds with a stimulation or depression of neuron activity. According to the authors, the test method used in the study is considered the safest and best qualitative and quantitative technique for measuring neuronal activity. However, the method does not differentiate direct or indirect effects of the substance being tested.

One isolated chemical fraction, termed "fraction 11," and an extract of valerian were shown to coordinate with the central nervous system depressant activity of valerian. Fraction 11 differed very little from other components in thin layer chromatographic patterns. The authors hope to elucidate the fractionated active component in a future publication. A possible mechanism of action may relate to the interaction of valerian constituents with the metabolism of gamma-aminobutyric acid in the brain (ESCOP, 1990). It should be noted that the testing procedures used by Krieglstein and Grusla do not rule out a synergistic effect of several components working in concert to produce the observed sedative effects established for valerian.

The question as to whether the pharmacological and therapeutic activity of botanical preparations results from a single chemical component, or a complex interaction of numerous compounds, again raises its head. The sedative activity of valerian appears, at least for the present, to result from a combination of direct relaxation of the smooth muscle and a depression of some centers of the central nervous system. Active components may involve various chemicals in the essential oil, one or more of the valepotriates, and the as yet unidentified water-soluble fractions noted by Krieglstein and Grusla (Houghton,

1988; Hobbs, 1989).

After the discovery of the valepotriates in the mid-1960s, and pharmacological studies of the early 1970s which attributed spasmolytic, sedative, and anti-convulsant activity to these compounds, many European valerian products were standardized to valepotriates (Hobbs, 1989). But obviously their discovery did not solve the challenge of determining the active components of valerian given the research findings of Krieglstein and Grusla (1988).

The German physician Rudolf Fritz Weiss puts the conflicting information into proper context: "Considerable difficulties arise when plant chemistry and pharmacology are applied to a medicinal plant on the one hand, and to the use and value of such a plant in practice on the other. These difficulties often seem insurmountable, particularly with a plant such as valerian where the actions are mainly in the mental sphere, so that animal experiments yield no convincing evidence, or at least none that will easily transfer to man. The valerian issue is therefore still very much under discussion" (Weiss, 1988, p. 283).

Scientific evaluation of valerian is further complicated by the relatively small number of published clinical studies. An Italian study by Delsignore *et al.* (1980) involved 40 patients with minor anxiety and emotional tension disturbances. They were randomized into two groups. Twenty patients received two 50 mg. Valerian tablets three times daily, while the other group received placebo. After 21 days, it was determined that valerian was statistically superior, and the absence of side effects confirmed its safety and efficacy in the treatment of emotional tension disturbances.

In the 1980s, P.D. Leathwood, F. Chauffard and other workers of a Nestlé research group published a number of clinical studies on the effects of valerian water extracts on sleep patterns. Valepotriates were absent from the preparations. Sleep quality was subjectively measured by the patient, and confirmed to some extent by EEG. The time taken to fall asleep was reduced, especially in older patients and insomniacs. Dream recall and nocturnal movement were apparently not effected. No drowsiness was reported the following morning (Chauffard *et al.*, 1982; Leathwood, *et al.* 1982; Leathwood and Chauffard, 1983; Williamson and Evans, 1988; Hobbs, 1989).

In one study (Leathwood *et al.* 1982) 128 volunteers reported subjective improvements in ratings for sleep quality and the time it took to fall asleep (sleep latency), but without producing a "hangover-like" effect, which is a common complaint of users of synthetic sedative drugs. In the study those who reported that they were habitually poor sleepers, or who took a long time to fall asleep, had the best results. Several authors have noted that one of the most appealing aspects of valerian as a sedative is that it does not interact with alcohol, as do barbiturates, and does not leave the user with a "hangover" in the morning. The authors conducted additional studies, with the ultimate conclusion that the extracts helped to significantly improve sleep quality of those suffering from mild insomnia, with minimal side effects.

Leathwood and Chauffard (1984) conducted a double-blind, randomized study which subjectively assessed sleep ratings. Movements were recorded throughout the night with wrist-worn activity meters. There was a significant decrease in sleep latency with dosages of 450 mg. of valerian compared to placebo. Doubling the dose produced no further improvement in sleep latency. A statistically insignificant number of patients (only eight) were involved in the study.

Safety

Cytotoxicity (cell attacking or destroying activity) and mutagenicity (mutation-causing activity) in animals cells has been reported for valepotriates, and, as a result, they have been studied (without positive results) as antitumor agents. The laboratory studies confirming cytotoxicity of valepotriates has aroused concern about the long-term safety of valerian preparations. Future formulations may be required to contain lower levels of valepotriates (Houghton, 1988). These studies have involved injectable forms of valerian, not oral dosages. *Valeriana officinalis* preparations are considered safe despite the known *in vitro* cytotoxic activity of valepotriates (ESCOP 1990). Acute side effects have not been reported. A study by Tufik, *et al.* (1984) examined the effects of valepotriates in female rats and their offspring. Oral dosage administration for a 30 day period did not produce changes in the average length of the estral cycle, nor the number of estrous phases and was deemed innocuous to pregnant rats and their offspring. For further information see: Houghton, 1988; Weiss, 1988; Hobbs, 1989; ESCOP, 1990; and Blumenthal, *et al.*, 1996.

Valerian is approved as a GRAS (generally recognized as safe) food ingredient in the United States. Extracts and the essential oil are used as flavoring components in alcoholic and nonalcoholic beverages, frozen dairy desserts, candy, baked goods, gelatins, puddings and meat products at an average maximum level of 0.01 percent (Leung and Foster, 1996).

In Germany a Commission E phytomedicine monograph (December, 1986) allows use of valerian in sedative and sleep-inducing preparations for states of excitation, and difficulty in falling asleep due to nervousness. (Blumenthal, *et al.*, 1996.)

Summary

Used for over 1,000 years, valerian extracts are now among the most popular sleep aids of Europe. Traditionally, valerian has been used to relieve muscle spasms, as a mild sedative, treatment for insomnia, hysteria, nervous tension, fatigue, and menstrual cramps. Over the past twenty or thirty years, well over 200 scientific studies on the active chemical components and their effects have been published in the scientific literature, especially in Europe. Experimental data indicates a rational scientific basis for mild sedative qualities, and spasmolytic activity. Additional studies suggest an ability to increase coronary blood flow, as well as mild pain-relieving qualities. Over 120 chemical components have been identified from the root and its essential oil. Questions remain as to the exact nature of active chemical components or fractions, and their specific pharmacological effects and mechanism of action. Despite the remaining questions, overwhelming evidence and clinical experience confirm the sedative effect of alcoholic extracts made from the fresh roots of *Valeriana officinalis*.

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GOLDENSEAL

Hydrastis canadensis



Steven Foster

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On the cover:

Goldenseal, *Hydrastis canadensis*. Photo ©1996 Steven Foster.

GOLDENSEAL

Hydrastis canadensis

by Steven Foster

Goldenseal (Hydrastis canadensis) has been one of the best-selling American medicinal plants in North American herb markets over the past 25 years. In addition, alkaloids from the plant are official in a number of world pharmacopoeias. Popular use is recorded from as early as 1798. Science confirms a rational basis for several of the dozens of traditional uses to which the plant or its preparations have been applied.

Nomenclature

The genus *Hydrastis*, generally placed in the buttercup family (Ranunculaceae) or sometimes a separate family (Hydrastidaceae), contains one monotypic species native to eastern North America. A number of modern texts including *Hortus Third*, Mabberly (1987), and Fernald (1950) mention the occurrence of another species in Japan. However, this refers to the monotypic *Glaucidium palmatum* Sieb. & Zucc. (*G. paradoxum* Makino, *Hydrastis jezoensis* Sieb ex Miquel). In Ohwi's *Flora of Japan* (1965), the above-mentioned synonyms are treated as a single species (*Glaucidium palmatum*).

Goldenseal (golden seal) is the common name under which the plant is best known. This name was adopted in the 1880 revision of the *United States Pharmacopoeia*. Previously, the plant had been known in commerce as yellow root, an ambiguous name referring to *Xanthorrhiza* and other plants. It has also been known as orange root, yellow puccoon, ground raspberry, eye-balm, and eye-root. As a dye plant it has been known as Indian paint, yellow paint, Indian dye, golden root, Indian turmeric, wild turmeric, curcuma (kurkuma), Ohio curcuma, wild curcuma, jaundice root, and yellow eye. The name goldenseal was introduced by the Thomsonians (adherents to the medical system of Samuel Thomson, 1769-1843). The small cup-like scars of previous annual stems, found on the upper side of the yellow rhizome, have the appearance of wax seals, once used to seal envelopes, hence the common name (Lloyd and Lloyd, 1884-85).

Based on a leaf specimen, the Swedish botanist, Linnaeus named the plant *Hydrophyllum verum canadense* in the first edition of *Species Plantarum* (1753). Since flowering or fruiting material was unavailable, he thought it to be a species of *Hydrophyllum* (Waterleaf). John Ellis later supplied Linnaeus with a flowering specimen. Linnaeus recognized it as a new taxon, which he named *Hydrastis* in the tenth edition of *System Naturale* (1759). The name "Hydrastis" is usually ascribed to Greek word origins, meaning "water" and "to act," generally believed to refer to medicinal effects on the mucuous membranes. J. U. and C. G. Lloyd (1884-85), however, believed this to be a misnomer, as neither Linnaeus or Ellis could have been aware of medicinal qualities of the plant. The Lloyds believed that Ellis, in fact, ascribed the derivation to a Greek word

meaning “imbibing of water,” referring to the erroneous early concept that the plant occurred in bog habitats. In 1759 Miller also published a colored illustration of the plant and a description, naming it *Warneria* (honoring Richard Warner). The French botanist Jussieu later changed it to *Warnera*. Linnaeus’s original name, however, was adopted, and the nomenclature has remained stable since the late eighteenth century (Lloyd and Lloyd, 1884-85).

Commerce and Conservation

The North American *Hydrastis canadensis* occurs in rich, moist, hilly woods from Vermont to Georgia, west to Alabama and Arkansas, north to eastern Iowa and Minnesota (Fernald, 1950). Goldenseal is an herbaceous perennial. Various botanical writers including Deam (1940), Fernald (1950), Gleason (1952), Strausbaugh and Core (n.d.), and Wofford (1989) note the rarity of the plant in various parts of the country where it once flourished due to over-collection of the root. As early as 1884-85, Lloyd and Lloyd noted dramatic declines in wild populations, to an extent as a result of root harvest, but more so as the result of habitat loss through deforestation. Lloyd and Lloyd (1884-85) quote George Merrell, “I think the root is becoming scarce, being gathered now, I am told, in small quantities, in isolated places here and there, where in former years it was found growing more like we have seen *Podophyllum* [Mayapple], in large patches.” The Lloyds note that Merrell is particularly qualified to speak on the subject as he headed the drug manufacturing firm started by his father, Wm. S. Merrell, who is credited with the introduction of goldenseal in commerce; at the time the Merrell firm was the heaviest consumer of *Hydrastis* in the world.

While over-harvesting may be blamed for supply shortages, the Lloyd brothers paint a complex picture of economic and social reasons for periodic shortages, providing arguments indicating that decrease in areas or populations is not necessarily accompanied by a decreased supply. They note that, historically, persons, such as farm laborers or poor classes of people collected the roots during times of economic hardship or during years of crop failure, and that fewer persons engaged in the collection of herbs during periods of economic prosperity or abundant crops. Being a minor commodity, factors would arise that would consume the entire supply in one season, causing shortages and a rise in price. This would stimulate more harvest the following season, causing subsequent market gluts and price decreases. Collectors or dealers were then left with overstocks which were sold at low cost, again providing a disincentive for harvest of the root during the following season. Collectors, they note, then turned their attention to other substances or pursuits. The price then stabilized, but stocks were exhausted, and then, as the Lloyds put it, “history repeats itself.” (Lloyd and Lloyd, 1884-85).

There are no figures to determine current supply and consumption of goldenseal. However, similar supply shortages and gluts with their attendant price fluctuations have been experienced in the past 15-20 years, just as they were 100 years ago. Reasons for recent shortages have included 1) harvesters shifting to digging of higher-priced commodities such as bloodroot (*Sanguinaria canadensis*), 2) recent periods of drought in the Southeast, which made digging difficult, 3) disinterest in harvest due to price fluctuations, and 4) lack of sufficient wild populations. Biological factors may also influence fluctuations in supply source. According to Lloyd (1912), hairlike rootlets,

traveling up to 3 feet from the parent plant produce adventitious buds which produce new plants. One theory is that, even after the main rhizome of a population is harvested, these buds may help to regenerate the population. However, no studies on population dynamics have confirmed this theory. Causes for year-to-year changes in population sizes may include differences in climatological conditions, and differences in state of development in which biomass might be expected to increase yearly (Eichenberger and Parker, 1976).

Historical development

The plant was utilized by a number of eastern North American Indian groups. The Cherokee used the roots as a wash for local inflammations, a decoction for general debility, dyspepsia, and to improve appetite. The Iroquois used a decoction of the root for whooping cough, diarrhea, liver trouble, fever, sour stomach, flatulence, pneumonia, and, with whiskey, for heart trouble (Moerman, 1986).

Benjamin Smith Barton refers to the use of goldenseal for rattlesnake bites as early as 1793 (Hobbs, 1990). In the first part of his *Collections for an Essay Towards a Materia Medica of the United States* (1798) under his discussion on *Heuchera americana* (p 8.) he makes one of the earliest observations of the occurrence of cancer among American Indian groups. "I am informed that the Cheerake [sic] cure it with a plant which is thought to be the *Hydrastis Canadensis*, one of our fine native dies [sic]." In the third part of his *Essay* (1804, p. 13), Barton notes, "The *Hydrastis* is a popular remedy in some parts of the United States." Among uses of the root Barton includes use as a bitter tonic (in "spirituous infusion") and as a wash for eye inflammations in a cold water infusion (Barton, 1798 and 1804). These uses have persisted to the present day. Further references to uses in the first half of the nineteenth century are extensively reviewed by Lloyd & Lloyd (1884-85), and further elaborated upon by Hobbs (1990).

Lloyd and Lloyd (1884-85) credit the popular introduction of the use of goldenseal to the Thomsonians (followers of the medical system developed by the self-taught practitioner Samuel Thomson, 1769-1843). It was, however, the Eclectic physician, John King (1813-1893) who the Lloyds credit for the first critical review of the therapeutic applications of goldenseal, thereby bringing it into general use among Eclectic physicians. King initially wrote about goldenseal in the first edition of *The Eclectic Dispensatory of the United States of America* (1852).

In nineteenth century pharmacy, goldenseal was listed among the official remedies in the first revision (1830) of the New York edition of *United States Pharmacopoeia*, but was absent in the Philadelphia edition of the USP published in the same year. According to Hobbs (1990) it was dropped in 1840, then became official again in USP from 1860-1926. It was recognized in the *National Formulary* in 1888, then again from 1936-1955.

Safety

Several works including Duke (1985), Foster and Duke (1990), and Westbrook and Preacher (1986) warn of a potential overdose of goldenseal (amount not specified) causing severe ulceration of any surface it may touch. Duke cites Tierra (1980) as the reference, but seems to use Millspaugh (1892) as well. Westbrook and Preacher cite Lust (1974). Turning to original references is always enlightening. Lust (1974) states:

“Eating the fresh plant produces ulcerations and inflammation of mucous tissue” (p. 206). In Westbrook and Preacher, citing Lust, that translates to “Irritation of mucous membranes with ulcerous secretions” (p. 61). One can trace these statements back to Millspaugh’s *American Medicinal Plants* (1892), “When taken in large doses *Hydrastis* causes a train of symptoms due to a hyper-secretion of the mucous membranes. If persisted in, it causes severe ulceration of any surface it may touch; and a catarrhal inflammation of mucous surface, followed by extreme dryness and fission (plant #9-3).”

To understand this in context, one must first turn to the title page of the first edition of Millspaugh (1887), subtitled “An illustrated and descriptive guide to the American plants used as homeopathic remedies...” Thus the “physiological action” as found in Millspaugh is the result of homeopathic “provings,” in which a substance is given in ultramolecular doses over a period of time to develop symptoms by which to match disease conditions. In this context, when used as a modern reference, all 180 plants treated by Millspaugh could be viewed as toxic. Peppermint, in Millspaugh, for example, causes “headache, with confusion; shooting pains in the region of the fifth-nerve terminals; throat dry and sensitive...[etc.].” If Dover Publications had not reprinted Millspaugh in 1974, it is likely that many of the comments in the modern literature relative to toxicity of goldenseal would never have been repeated out of their original context. The title page of the Dover reprint neglects the original homeopathic subtitle of Millspaugh. When one traces back to Millspaugh’s own cited references, the physiological action seems to be abstracted from E. M. Hale’s “the homeopathic uses of *Hydrastis canadensis*,” pp. 161-169, in Lloyd and Lloyd (1884-85), as well as Hale’s *New Remedies* (1864), in which Hale decries the use of a topical mixture of *Hydrastis* with the caustic, chloride of zinc, and the narcotic, stramonium ointment (*Datura*).

Modern use

According to Hobbs (1990) and Brevoort (1995), goldenseal is among the top-selling herbs in the American health food market. Uses are numerous, including, but not limited to antiseptic, hemostatic, diuretic, and laxative, and tonic/antiinflammatory for inflammations of the mucous membranes. It has also been used for hemorrhoids, nasal congestion, mouth and gum sores, and eye afflictions; externally for wounds, sores, acne, ringworm, and other ailments (Leung and Foster, 1996). Duke (1985) lists the greatest number of uses in the modern literature. He notes that *Hydrastis* extracts and hydrastine hydrochloride are still used as a component in collyriums (eye washes). Tyler (1985), recording folk uses in Indiana, notes the use of *Hydrastis* in spring tonics for cancer (type not specified), and especially as a rinse (root tea) to relieve sore mouth, cracked and bleeding lips, and chewed for the treatment of canker sores. He notes that it was frequently and enthusiastically recommended by informants for the treatment of sore mouth and related problems. A teaspoon of the powdered root, mixed in a glass of water, was recorded as a folk remedy for sore throat, stomach troubles, and the root tea for stomach ulcers and any pains of the stomach. The leaves were also used macerated in vinegar for snake bite, and the fresh leaf juice taken for “fits.”

King (1977) records similar usage in the Missouri Ozarks. The roots, mixed in water, are recorded as an eye wash, and also are used for sore gums. Added to mineral oil, it is taken daily for stomach ulcers. Small pieces of the fresh chopped roots mixed

with maple syrup or molasses are rubbed in the mouth to treat babies with “thrash” [thrush].

Very little pharmacological research has been conducted on *Hydrastis* over the past 40 years, and even in this century. The most recent comprehensive review of the pharmacology and therapeutics of *Hydrastis* and its alkaloids was by Shideman (1950), who noted that little work had been done in the previous 40 years.

According to Genest and Hughes (1969), the major alkaloids of goldenseal are hydrastine (2-4%) and berberine (2-3%), with smaller amounts of canadine and hydrastinine. The major pharmacological effects are attributed to hydrastine and to a lesser extent berberine. Actions of hydrastine (as an intravenous injection of its hydrochloride in animal experiments) include decrease in blood pressure and stimulation of involuntary muscles. Canadine has been reported to act as a uterine stimulant in various animal models. Berberine has been reported to have stomachic and hemostyptic action (Genest and Hughes 1969) plus it stimulates secretion of bile in humans, lowers blood pressure in laboratory animals, is antibacterial, and has numerous other activities. The pharmacological properties of berberine resemble those of hydrastine (Leung and Foster, 1996).

Most recent scientific reports including Datta, Bose and Ghosh (1971), Zwaving and de Jong-Havenga (1972), and El-Masry, Korany and Abou-Donia (1980) have focused on methods for determination of *Hydrastis* alkaloids in various pharmaceutical preparations. As of 1969, goldenseal was official in the French Pharmacopoeia as well as at least twelve other pharmacopoeias (Genest and Hughes, 1969). In 1982 the alkaloid, hydrastine, was still official in the pharmacopoeias of nine countries (Hobbs, 1990). Products containing *Hydrastis* have been recommended as tonics, stomachics, antacids, and antispasmodics for gastritis, colitis, varicose veins, menstrual difficulties, sore mouth and other local irritations, and other uses (Genest and Hughes, 1969).

One modern folk use has been the consumption of goldenseal as a means to mask urine tests for illicit drugs. This grows out of a fictional plot of *Stringtown on the Pike*, a John Uri Lloyd novel (Lloyd, 1900). There is no scientific evidence to support this use; in fact, it may instead promote false-positive readings (Tyler, 1993; Foster, 1989).

Summary

The popular use of goldenseal is recorded as early as 1798. Its popularity grew in the 1830s. Clinical recognition of the use of goldenseal came in the 1850s and it continued to be officially recognized in the U.S. until 1960. During the 1970s and 1980s goldenseal regained wide use among the herb-consuming public. Given its long history of domestic use, without reports of toxicity, other than those misextrapolated from historical homeopathic literature, there seems to be a reasonable certainty of safety for acute applications. Much more modern research is needed to confirm mode of action, best dosage forms, and general biology of the plant itself. Efforts have been made recently to study population dynamics and develop cultivated sources of supply (Davis, 1996).

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MILK THISTLE

Silybum marianum



Steven Foster

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On the cover:

Milk Thistle, *Silybum marianum* Photo ©1996 Steven Foster.

MILK THISTLE

Silybum marianum

by Steven Foster

Milk thistle (Silybum marianum (L.) Gaertner), a member of the Aster family (Asteraceae or Compositae), is a widespread wayside herb of uncultivated ground and waste places throughout much of Europe. The plant, carried to North America by European colonists at an early date (Pickering, 1879), is naturalized in the Eastern United States, California, and South America. In the last 30 years milk thistle seed extracts have been intensively researched, confirming its 2,000 year old therapeutic use in liver disease.

Nomenclature

“Milk thistle” has emerged as the most widely known English common name for the plant. Older works list it as Mary thistle, St. Mary thistle, Marian thistle, Lady’s thistle, and Holy thistle (not to be confused with Blessed thistle, *Cnicus benedictus*). Latin synonyms include *Carduus marianus* L. and *Cnicus marianus*. *Silybum* derives from a name applied to some edible thistles by the first century Greek physician Dioscorides. The genus contains two species. The other species is *S. eburneum*, indigenous to the Mediterranean region. The specific name *marianum* preserves the legend that the white mottling of the leaves was caused by a drop of the Virgin Mary’s milk (Nicholson, 1886-87). The plant is also traditionally used as a galactagogue (stimulating milk production), perhaps contributing to word origins of the common name.

Food Use and Safety

In European gardens the plant has been cultivated as a vegetable. It was still grown in old-fashioned British gardens at the end of the nineteenth century (Henderson, 1889). The young leaves (with spines removed) were used in spring salads and as a spinach substitute. Young stalks, peeled and soaked, are eaten like asparagus. The roots, soaked in water overnight to remove bitterness, are eaten like salsify. Milk thistle’s flower receptacle, resembling an artichoke, was cooked and eaten like artichokes (Hedrick, 1919; Grieve, 1931). Roasted seeds have been employed as a coffee substitute (Uphof, 1968). Adverse effects from ingesting any plant part are generally lacking from the literature. Animal experiments have shown that seed extracts are safe, even in large doses, with practically no side effects, as well as no embryo toxic effect (Weiss, 1988). Adverse effects in human studies with the seed extract (silymarin) are also generally absent (Der Marderosian and Liberti, 1988). A mild laxative effect has been observed in isolated cases (Blumenthal, *et al.*, 1996).

Medical History

In one form or another, various preparations of milk thistle, especially the seeds, have been used medicinally for over 2,000 years. In modern research scientists often attempt to find new biologically active plant substances through random screening methods. However, *Silybum* is a classic example of the value of utilizing historical records for the development of modern herb products. Its use as a liver-protecting agent dates to early Greek references. The first century Roman writer Pliny the Elder (A.D. 23-79) noted that the juice of the plant mixed with honey is excellent for “carrying off bile” (Jones, 1966). Historical references on the plant are particularly abundant in the herbal literature of the Middle Ages, including the anti-liver toxic activity of the seeds (Halbach, 1976).

While native to Southern Europe, the plant was found in England by the end of the sixteenth century. Grieve (1931) quotes Gerard (1597), “My opinion is that this is the best remedy that grows against all melancholy diseases” [diseases of the liver].

The British herbalist, Nicholas Culpepper (1787 ed.) notes that it is effectual “to open the obstructions of the liver and spleen, and thereby is good against the jaundice.” He also writes, “The seed and distilled water are held powerful to all the purposes aforesaid, and besides, it is often applied both inwardly to drink, and outwardly with cloths or sponges [sic], to the region of the liver, to cool the distemper thereof....”

The plant is absent from most American works on medicinal plants until the end of the nineteenth century. Eclectic physicians Felter and Lloyd (1898) list the seeds as *Carduus marianus*. They write, “[It] is an old remedy which had nearly passed out of use and has more recently been revived.” They also state, “Congestion of the liver, spleen, and kidneys is relieved by its use.”

A tincture of the whole plant is an official preparation of the first *United States Homeopathic Pharmacopeia* (Anon. 1878). In homeopathy the seed tincture is used for liver disorders, jaundice, gall stones, peritonitis, coughs, bronchitis, varicose veins, and congestion of the uterus (Schauenberg and Paris, 1977). A 1985 German monograph on the use of *Silybum marianum* in homeopathy includes indications for diseases of the gall bladder and liver.

Modern Medicinal Use

Intensive research in the hepatoprotectant (liver protecting) effects of milk thistle began about 40 years ago. In Germany, milk thistle seed extracts have been marketed for many years. Attempts to isolate the primary active chemical components were under way by 1958, but there had been few attempts to characterize the chemical components prior to 1965 (Vogel, 1976). Wagner *et al.* (1968) first isolated silymarin from the seeds, providing an opportunity for establishing a scientific basis for use in treating liver diseases. Later it was found that silymarin was not a single component, but a mixture of complex compounds known as flavonolignans. Silymarin is found in concentrations of 4 to 6 percent in the ripe seeds (Der Marderosian and Liberti, 1988). The first chemical compounds isolated and structurally characterized were silybin, silydianin, and silychristin (Wagner and Seligmann, 1985). A number of other flavonolignans have also been found in the seeds, in addition to apigenin, silybonol, and myristic, palmitic, stearic, and oleic acids (Der Marderosian and Liberti, 1988).

Compared with silymarin, few plant principles have been as extensively investigated in recent years (Weiss, 1988). Research using animal models has demonstrated

liver-protectant effects of proprietary German seed extracts, and extensive clinical, histological, and laboratory data have confirmed the efficacy of silymarin (Weiss, 1988). Early pharmacological studies by Keppler *et al.* (1968) and Hahn *et al.* (1968) showed that silymarin has a protective effect on the liver when exposed to various toxic compounds in laboratory models. The liver-protectant activity of silymarin has been demonstrated in numerous experimental models of toxic liver damage, including damage from carbon tetrachloride, galactosamine, thioacetamide, hepatotoxic cold-blood frog virus (FV3), lanthanides, and the poisonous substances of the death cap fungus, phalloidin and alpha-amanitin (Blumenthal, *et al.*, 1996). Further studies have suggested that pretreatment with silymarin inhibits alcohol-induced liver damage and has also established pharmacological mechanisms for the inhibitory action, including scavenging of free radicals, leukotrienes, and an ability to stimulate liver protein synthesis. These studies are reviewed by Hikino and Kiso (1988).

The therapeutic efficacy is based on several separate mechanisms of action. Silymarin alters the outer liver membrane cell structure in such a way that certain toxins, as demonstrated with the toxins of the death cap fungus, cannot enter the cell. Silymarin also stimulates RNA polymerase A (also known as polymerase I), enhancing ribosome protein synthesis, resulting in activating the regenerative capacity of the liver through cell development. Clinical use of silymarin today applies to toxic liver damage for the supportive treatment of chronic inflammatory liver disorders and cirrhosis of the liver, such as in chronic hepatitis, and fatty infiltration of the liver by alcohol and other chemicals (Blumenthal, *et al.*, 1996).

Remarkable studies have shown that certain milk thistle preparations can produce both a protective and curative effect on liver damage resulting from the highly toxic compounds, phalloidin and alpha-amanitin (from the death cap *Amanita phalloides*, one of the most deadly of poisonous mushrooms). Poisoning from ingestion of the mushroom, given its severe damage to the liver, has been very difficult to treat (Weiss, 1988). Vogel and Temme (1969) note that earlier experiments showed that silymarin had an anti-hepatotoxic (anti-liver toxic) effect, when it was administered before poisoning by phalloidin. In their 1969 study, Vogel and Temme showed a curative anti-hepatotoxic effect when silymarin was administered after exposure to phalloidin, establishing a model for therapeutic use in humans. This study suggested that silymarin could both prevent and cure liver damage. Silymarin was considered to have high anti-hepatotoxic activity, given the fact that phalloidin is one of the substances most toxic to the liver. The anti-hepatotoxic effect of silymarin was found to be dependent upon the time interval in which poisoning and therapy took place, as well as the degree of liver damage. It is suggested that silymarin prevents penetration of the two *Amanita* toxins by competing with the toxins for the same receptor on cell membranes (Hikino and Kiso, 1988).

A multicenter trial involving 220 cases of *Amanita* poisoning treated in German, French, Swiss, and Austrian hospitals was carried out from 1979 to 1982 using silibinin in supportive treatment. (Silibinin, the product form used in the above studies, is a water soluble compound derived from milk thistle seeds that is used in intravenous infusion therapy. It should not be confused with the oral dosage forms of silymarin.) According to the author of the study, Karl Hruby of the University of Vienna Poison Information Center, the mortality rate was 12.8 percent. This compares with a mortality rate of 22.4 percent carried out in a study involving 205 patients by Floersheim *et al.* (1982), in which only 16 patients were treated with 20 to 50 mg/kg/day of silibinin. Hruby (1984)

concluded that the use of silibinin as an adjunct to current methods of treating *Amanita* poisoning can lower mortality rates below any levels which have previously been achieved.

A follow-up biopsy study by G. Poser (1971) reported that 67 subjects who had been treated as out patients for toxic-metabolic liver damage, chronic hepatitis, and bile duct inflammation showed a drop in chemical parameters associated with liver disease. Chronic hepatitis was biotically found to be significantly improved after three months of silymarin administration (525 mg/day of silymarin). Conditions associated with bile duct inflammation responded particularly well.

In several controlled trials the hepatoprotective effects of silymarin in toxic liver disease could be demonstrated as accelerating normalization of impaired liver function. In a double-blind study conducted by Fintelmann and Albert (1980), 66 patients, mainly with alcohol-induced toxic liver disease, received either silymarin (420 mg/day) or a placebo for a four week period. Patients who received silymarin showed an accelerated improvement of increased serum levels of liver enzymes GOT (glutamic-oxalacetic transaminase), GPT (glutamic-pyruvic transaminase) and Gamma-GT (gamma-glutamyl-transpeptidase).

Several other placebo-controlled double-blind studies in alcohol- and drug-induced liver disease showed a clear superiority of treatment with 420 mg silymarin for 4 to 8 weeks compared with placebo (Di Mario, 1981; Feher and Lang, 1988; Salmi and Sarna, 1982). In a further double-blind study with 36 patients suffering from alcohol-induced liver disease, pathological liver parameters (GOT, GPT, Gamma-GT, and bilirubin) were significantly reduced after 6 months of treatment with silymarin compared to placebo (Feher *et al.*, 1990).

References cited above represent a small sampling of the dozens of clinical studies that have been conducted on silymarin. Double-blind studies on the effect of silymarin on toxic liver damage (mostly induced by alcohol), chronic liver disease, and disease caused by psychopharmaceuticals are reviewed by Hikino and Kiso (1988). They concluded that basic laboratory and clinical data suggest that silymarin is a therapeutically useful medicinal plant product that stabilizes the cell membrane and stimulates protein synthesis while accelerating the process of regeneration in damaged liver tissue, and that these effects are important in the therapeutic efficacy of silymarin.

According to a recent review article by Morazzoni and Bombardelli (1995), in Germany, the primary causes of liver intoxication include alcohol (71 percent), psychopharmaceuticals (18 percent), and industrial exposure to chemicals (11 percent). While removal of the liver disease-causing substance is important in management of toxic liver situations, silymarin is the best documented drug for treatment of liver intoxication. Previously, oral clinical application of silybin has been limited by bioavailability. These authors report on a new silybin complex that has been shown to have markedly improved bioavailability. These authors report on a new silybin complex that has been shown to have markedly improved bioavailability, hence pharmacodynamic activity in both animal and human studies.

While silymarin has primarily been used as a phytomedicine, recent studies reviewed by Morazzoni and Bombardelli (1995), suggest future use in dermatological and cosmetic products based on a number of activities including promoting healing at wound sites, improved burn healing, and counteracting skin degeneration and aging via antiinflammatory and free radical scavenging mechanisms.

Summary

For over 2,000 years Europeans have used milk thistle seeds as an herbal treatment for liver disorders. The plant has been grown both as an ornamental and a vegetable. Virtually all parts of the plant have been used as food with no reports of toxicity. Over the past 40 years, intensive chemical, pharmacological, and clinical research has confirmed mechanisms of action and therapeutic value of silymarin in a wide range of human liver disease including toxic metabolic liver damage (such as fatty degeneration of the liver) and supportive treatment of chronic hepatitis and cirrhosis. Silymarin, derived from the seeds of the plant, has shown both protective and restorative effects in liver disease. Other components of the seed have proven useful in supportive therapy for deathcap mushroom poisoning. The plant is a primary example of the usefulness of using historical efficacy as a starting point for the development of modern applications for medicinal plants.

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